S.H. Gage

STUDIES

FROM

THE BENDER
Hygienic Laboratory

ALBANY, N. Y.

REPRINTS

Volume I

1904

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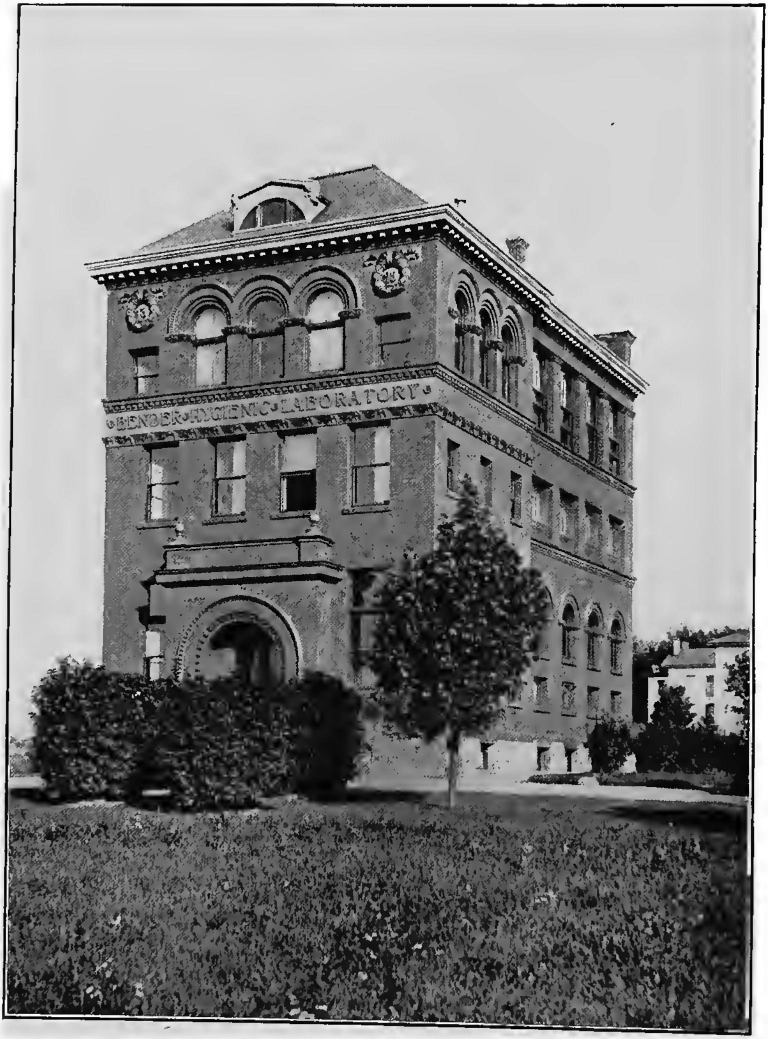

THE BENDER HYGIENIC LABORATORY

STUDIES
FROM
THE BENDER
HYGIENIC LABORATORY

ALBANY, N. Y.

HISTOLOGY & EMBRYOLOGY
CORNELL UNIVERSITY.

REPRINTS

VOLUME I

1904

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HINDER HYGIENIC LABORATORY
INCORPORATED
1896

The Organization *of* the Laboratory

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Trustees

Dr. A. Vander Veer
Dr. Henry Hun
Dr. George E. Gorham
Hon. Robt. G. Scherer
Harry H. Bender

Director

Richard M. Pearce, M.D.

Assistants

E. MacD. Stanton, M.D.
Charles K. Winne, Jr., M.D.

Assistant Chemist and Bacteriologist
(*In charge of the Albany Filtration Plant*)

Leonard M. Wachter

Voluntary Assistants

Ellice McDonald, M.D., 1903-'04
Edwin F. Sibley, M.D., 1904-'05

In Connection with the Laboratory Courses of the Albany Medical College

Richard M. Pearce, M.D., *Professor of Pathology and Bacteriology*
E. MacD. Stanton, M. D., *Lecturer in Normal Histology and in the Anatomy of the Nervous System*
Arthur W. Elting, M.D., *Lecturer in Surgical Pathology*
Arthur T. Laird, M.D., *Lecturer in Clinical Microscopy*
Herbert D. Pease, M.D., *Lecturer upon Antitoxins and Immunity*
Charles K. Winne, Jr., M.D., *Instructor in Bacteriology*
H. Judson Lipes, M.D., *Instructor in Obstetrical Pathology*
Harry W. Carey, M.D., *Instructor in Surgical Pathology*
Edwin F. Sibley, M.D., *Instructor in Clinical Microscopy*
Donald Boyd, M.D., *Demonstrator of the Anatomy of the Nervous System and Assistant in Normal Histology*

Stenographer

Miss Maude Marshall

Preparator

Miss Helen R. King

Janitor

J. E. G. Roy

NOTE

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THIS volume comprises the publications of the Bender Hygienic Laboratory for the year 1903-'04. These have appeared in various medical journals, but for the sake of uniformity in paper and press work, the reprints have been taken from the Albany Medical Annals. The object of again presenting these studies is to bring them in collected form before those especially interested in the laboratory or its work. As this is the first attempt to establish an annual publication, which shall adequately represent the work of this institution, a short historical sketch of the origin and development of the laboratory, with a list of previous publications, has been included.

RICHARD M. PEARCE,
Director.

THE BENDER HYGIENIC LABORATORY
ALBANY, N. Y., *November*, 1904.

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RICHARD M. PEARCE, M.D.

MATTHEW W. BENDER

Reprinted from ALBANY MEDICAL ANNALS, November, 1904

HISTORY OF THE BENDER HYGIENIC LABORATORY

By GEORGE E. GORHAM, M. D.

On June 27th, 1895, the corporation of the Bender Hygienic Laboratory was formed, the members being: Mr. Matthew W. Bender, Dr. Albert Vander Veer, Dr. George E. Gorham, Dr. Henry Hun and Hon. Robert G. Scherer.

The corporation was organized to take over from Mr. Bender twenty thousand dollars, a sum which Mr. Bender had offered to give for the erection of a laboratory building upon the condition that a suitable site be furnished. The board of trustees was immediately elected, and to its care were entrusted the generous gift of Mr. Bender and the carrying out of his wishes in securing a suitable site and erecting the building. A grant from the city of Albany for the spacious and beautiful grounds on Lake avenue now occupied by the laboratory was promptly obtained. Messrs. Fuller and Wheeler were employed as architects, and under the special supervision of Mr. Harry H. Bender the building was completed and dedicated on October 27th, 1896.

Dr. George Blumer, of the Johns Hopkins Hospital, was appointed director and under his supervision the laboratory was fully equipped with necessary apparatus. About one hundred microscopes, necessary tables, lockers, etc., were placed in the class rooms; steam and hot air sterilizers, microtomes, thermostats, freezing apparatus, etc., were added for general pathological and bacteriological work.

This generous outlay for the equipment of the laboratory was furnished by the faculty of the Albany Medical College. Such, briefly, is the history of the conception and birth of the Bender Hygienic Laboratory. Sixteen months from the time the subject was first presented to Mr. Bender for his consideration by his family physician the building was completed, and opportunity for one of the most important scientific works in the history of Albany was given.

The first director of the laboratory, Dr. George Blumer, and his assistants, Dr. Lartigau, Dr. Elting, Dr. Carey and Dr. Laird, under the direction of the Albany Medical College, arranged and carried out a course of instruction in pathology, bacteriology, histology and microscopy for the students of the Albany Medical College. These valuable courses of instruction are continued throughout each college year. They are, in fact, part of the regular curriculum of the Albany Medical College, and classes of forty or fifty students take the different courses annually. Dr. Blumer resigned in 1903, and the work has been continued by his successor, Dr. Richard M. Pearce, assisted by Drs. Stanton and Winne.

The Albany filtration plant for filtering Albany's water supply is under supervision of the laboratory, and daily examinations of the water are made.

By special contract with the city of Albany cultures from all cases of suspected diphtheria are examined and reported to the attending physician. Sputum from suspected cases of tuberculosis is also examined. Work of the same character is done for the State Department of Health of New York.

The examination of milk and water supplies in case of epidemics throughout the State is a part of the work done at the laboratory.

Hundreds of examinations of pathological specimens, blood, sputum and urine are annually made for the hospitals of Albany, while physicians in the surrounding country are constantly sending specimens for examination.

Added to this general work of the laboratory is special research work, some forty papers having been published during Dr. Blumer's directorate, and eleven during the past year by the present staff.

Thus may be sketched in a few words the scope of the work of the Bender Laboratory. But these words indicate only inadequately the importance of this institution and the great value for years to come of the gift of Mr. Bender in promoting the health and welfare of the community.

LIST OF PUBLICATIONS FROM THE BENDER HYGIENIC LABORATORY, FROM 1896 TO 1903.

GEORGE BLUMER, M. D.

1—Diseases Which Can be Directly Traced to Contaminated Drinking Water, ALBANY MEDICAL ANNALS, March-April, 1897.

2—Primary Round Cell Sarcoma of the Epididymis, ALBANY MEDICAL ANNALS, December, 1897.

3—Adeno-myoma of the Round Ligament, *American Journal of Obstetrics,* no. 1, 1898.

4—Tuberculosis of the Stomach, ALBANY MEDICAL ANNALS, March, 1898.

5—A System of Classification of Pathological Material, ALBANY MEDICAL ANNALS, November, 1898.

6—A Case of Post-typhoid Bone Inflammation Due to the Colon Bacillus, *The Pacific Record of Medicine and Surgery,* November 15, 1898.

7—Tuberculosis of the Aorta, *American Journal of the Medical Sciences,* January, 1899.

8—A Case of Mixed Puerperal and Typhoid Infection, *American Journal of Obstetrics,* no. 1, 1899.

9—The Present Status of the Widal Reaction, ALBANY MEDICAL ANNALS, January, 1899.

10—A Third Case of Tuberculosis of the Aorta, ALBANY MEDICAL ANNALS, May, 1899.

11—The Relation of Trauma to Tuberculosis, ALBANY MEDICAL ANNALS, November, 1899.

12—The Infectious Character of Tuberculosis and the Prognosis of Incipient Consumption, ALBANY MEDICAL ANNALS, April, 1900.

13—Hæmorrhagic Infection in an Infant Due to the Typhoid Bacillus, *Journal of the American Medical Association,* December 29, 1900.

14—Bilateral Cholesteatomatous Endotheliomata of the Choroid Plexus, *Welch's Festchrift,* 1900.

15—Further Notes on Abnormalities of the Urinary System, ALBANY MEDICAL ANNALS, January, 1901.

16—The Bacteriology of Lobar Pneumonia Especially in Adults, ALBANY MEDICAL ANNALS, August, 1901.

17—The Present Status of the Infectious Theory of Malignant Neoplasms, *New York State Journal of Medicine,* November, 1901.

18—Some Aspects of the Pathology of the Pancreas, *Medical News,* August 9, 1902.

19—A Note on the Embryonal Glandular Tumors of the Kidney, ALBANY MEDICAL ANNALS, August, 1903.

20—The Relation of the Status Lymphaticus to Sudden Death, etc., *Johns Hopkins Hospital Bulletin,* October, 1903.

With W. H. HAPPEL, M. D.

21—A Case of Pulmonary Tuberculosis Associated with Round Ulcer of the Stomach, ALBANY MEDICAL ANNALS, December, 1898.

With L. H. NEUMAN, M. D.

22—Report of a Family Outbreak of Trichinosis, *American Journal of the Medical Sciences,* January, 1900.

With A. J. LARTIGAU, M. D.

23—A Report of Three Cases of Ascending Urinary Infection Due to Bacillus Pyocyaneus and the Proteus Vulgaris, *New York Medical Journal,* September 22, 1900.

With A. T. LAIRD, M. D.

24—Hæmorrhagic Infection Due to the Bacillus Mucosus Capsulatus, *Johns Hopkins Hospital Bulletin,* February, 1901.

With W. KIRK, JR., M. D.

25—A Case of Periostitis of the Seventh Rib Occurring During the Course of Typhoid Fever, ALBANY MEDICAL ANNALS, January, 1901.

With J. M. MOSHER, M. D.

26—Hyperplasia of the Pituitary Body with Eburnation of the Skull. ALBANY MEDICAL ANNALS, March, 1901.

With A. MACFARLANE, M. D.

27—Report of an Epidemic of Noma, *American Journal of the Medical Sciences,* November, 1901.

With H. L. K. SHAW, M. D.

28—A Case of Appendicitis in an Infant Seven Weeks of Age, *Archives of Pediatrics,* August, 1901.

With H. C. GORDINIER, M. D.

29—A Case of Chronic Lymphatic Leukæmia Without Enlargement of the Lymph Nodes, *Medical News,* October 31, 1903.

AUGUST J. LARTIGAU, M. D.

30—The Bacillus Pyocyaneus as a Pathogenic Factor in Human Pathology, with Report of Three Cases, *Philadelphia Medical Journal,* September 17, 1898.

31—A Contribution to the Study of the Pathogenesis of B. Pyocyaneus, with Especial Reference to its Relation to an Epidemic Dysentery, *Journal of Experimental Medicine,* 1898, vol. III, no. 6.

32—A Contribution to the Study of the Micrococcus Tetragenus in Acute Angina, *Philadelphia Medical Journal,* April 22, 1899.

33—On Typhoid Septicæmia, with the Report of Two Cases, one of Which was a Typhoid Infection Without Intestinal Lesions, *Johns Hopkins Hospital Bulletin,* April, 1899.

34—Typhoid Infection of the Uterus, *New York Medical Journal,* June 16, 1900.

With A. MACFARLANE, M. D.

35—Acute Angina Due to Micrococcus Tetragenus, *Journal of the American Medical Association,* June 24, 1899.

With H. C. GORDINIER, M. D.

36—A Report of a Case of Typhoid Pleurisy, *American Journal of the Medical Sciences,* January, 1901.

ARTHUR W. ELTING, M. D.

37—The Acute Pneumonic Form of Tuberculosis, *American Journal of Medical Sciences,* May, 1900.

38—The Bacteriology of Gonococcus Infections, ALBANY MEDICAL ANNALS, March, 1900.

39—Intermittent Gastric Hypersecretion, *Boston Medical and Surgical Journal,* May, 1900.

40—Primary Carcinoma of the Vermiform Appendix, with a Report of Three Cases, *Annals of Surgery,* April, 1903.

George Blumer.

DIRECTOR OF THE BENDER HYGIENIC LABORATORY, 1896-1903

With A. VANDER VEER, M. D.

41—Resumé of the Subject of Actinomycosis with Report of a Case of Abdominal Actinomycosis, ALBANY MEDICAL ANNALS, January, 1903.

HARRY W. CAREY, M. D.

42—Report of Two Testicular Teratomata with a Review of the Recent Literature, *Johns Hopkins Hospital Bulletin,* November, 1902.

43—The Presence of the Shiga Variety of Dysentery Bacilli in an Extensive Epidemic of Dysentery, *Journal of Medical Research,* March, 1903.

ARTHUR T. LAIRD, M. D.

44—Recent Studies Regarding the Morphology of the Diphtheria Bacillus, ALBANY MEDICAL ANNALS, 1903, xxiv, 251.

With CHARLES E. DAVIS, M. D.

45—A Case of Diphtheria, ALBANY MEDICAL ANNALS, 1901, xxii, 499

HARRIS MOAK, M. D.

46—On the Occurrence of Carcinoma and Tuberculosis in the Same Organ or Tissue, *Journal of Medical Research,* 1902, viii, 128.

THOMAS G. DICKSON, M. D.

47—Concerning the Nature of the Small Cysts Frequently Found in the Peritoneum Covering the Fallopian Tubes, *American Journal of Obstetrics*, 1903, xlviii, no. 1.

Reprinted from ALBANY MEDICAL ANNALS, November, 1904.

ANNUAL REPORT OF THE DIRECTOR FOR THE YEAR ENDING AUGUST 31, 1904.

To the Trustees of the Bender Hygienic Laboratory:

I have the honor to submit my report for the year ending August 31, 1904.

Organization—The equipment of the laboratory and the organization of its work by my predecessor, Dr. George Blumer, were such that upon September 1st, 1903, I was able to enter upon my duties under the most favorable circumstances. The staff of the laboratory was immediately completed by the appointment, as assistants, of Edwin MacDonald Stanton (Iowa State College, B. S., 1898; University of Pennsylvania, M. D., 1903) and of Charles Knickerbacker Winne, Jr., (Johns Hopkins University, A. B., 1897; M. D., 1901). Early in the year it was evident that the clerical work had increased to such an extent that the full time of a stenographer would be required; and with your approval this service has been provided. It was also found that much valuable time was consumed by the members of the staff in semi-technical work which could be done as well at a moderate cost by a non-medical assistant. By arrangement with the faculty of the Albany Medical College the additional salary was guaranteed and the appointment was made. Both of these changes have aided greatly in the routine work of the laboratory.

Mr. Leonard M. Wachter was reappointed for the year 1904-'05 as assistant chemist and bacteriologist, in charge of the Albany filtration plant.

The Work of the Laboratory—This may be conveniently divided into routine examinations, under-graduate teaching, instruction to special students and original investigations.

The nature of the routine work of the laboratory is shown in the accompanying table which gives the source of the material and the number and character of the examinations. This table does not include the bacteriological studies carried out in connection with the autopsy work, the tests made for the milk committee of the Albany County Medical Society, or the examinations of "winter-killed" deer, made during the past winter for the New York State Forestry, Fish and Game Commission. Mr. Wachter's report of his chemical and bacteriological examinations, made at the filtration plant, have been included in his annual statement to the Water Bureau of the City of Albany and do not appear in this report.

TABULATION OF THE ROUTINE EXAMINATIONS MADE AT THE BENDER LABORATORY FROM SEPTEMBER 1, 1903, TO AUGUST 31, 1904

	State Dep't. of Health	City Board of Health	Albany Hospital	St. Peter's Hospital	Child's Hosp. and St. Margaret's House	Albany Orphan Asylum	Alms House	Coroner's Physicians	Physicians	
Sputum	272	35			2				32	341
Widals	106	10	77	5	2	2			34	226
Throat cultures	729	713				83			142	1667
Water, milk and ice	407		3		1	1			46	458
Miscellaneous examinations	5		52	2	2				69	130
Surgical specimens			939	19	3				42	1003
Autopsies			42	1	10	6	8	31	25	123
	1519	758	1113	27	20	92	8	31	390	3958

The examination of surgical specimens has been greatly facilitated by the general adoption of Wright's frozen section method which ensures the surgeons of an early report and also lessens the daily labor in the laboratory. The custom adopted by the Albany Hospital, at our suggestion, of forwarding with each specimen a printed form upon which is entered the important data concerning the tissue to be examined allows a more intelligent examination, and also enables us to keep more complete laboratory records. As will be seen by the accompanying table, the examination of material from the surgical service of the Albany Hospital constitute a large share of our routine work. For the performance of this work the hospital contributes neither service nor money. It has occurred to me that hospital and laboratory alike would be greatly benefited by the appointment of a pathological house officer whose duty it would be to assist in that part of the hospital work carried on in the laboratory. In return for this service the hospital should furnish him with room and board. This assistant should be a graduate in medicine and preferably one with post-graduate hospital training. Such an arrangement has been practiced for years at the Boston City Hospital which indeed has two pathological internes and in that institution has proved most satisfactory. I believe it might profitably be adopted by the Albany Hospital and respectfully suggest it to your board.

I wish also to call your attention to the great increase in the amount of work done for the State Department of Health. This increase of work has not been accompanied by an increase of appropriation; and the labor is out of all proportion to the compensation. I think an effort should be made to secure a larger appropriation. The rapid development of this work is shown in the following table, which is based on examinations made from September 1, to August 31st.

	Throat cultures	Sputum	Widal reactions	Water, milk, ice and sewage
1901-'02	222	33	11	90
1902-'03	807	71	50	184
1903-'04	729	256	123	412

The laboratory courses given during the past year (term of seven and a half months) to undergraduates of the Albany Medical School are as follows:

Pathology and bacteriology—Drs. Pearce, Stanton and Winne, eight and a half hours a week.

Normal histology—Drs. Stanton and Winne, six hours a week.

Clinical microscopy—Dr. Laird, two and a half hours a week.

Surgical pathology—Drs. Elting and Carey, two and a half hours a week.

Histology and pathology, in connection with the course in obstetrics—Dr. Lipes, two and a half hours a week.

Anatomy of the nervous system—Dr. Becker, one hour a week.

For the year 1904-'05 several changes have been made in these courses. The need of more detailed instruction in the methods of clinical microscopy has led to the division of this class into two sections and the appointment of another assistant, Dr. E. F. Sibley. The course in the anatomy and pathology of the nervous system has been placed under the direction of Dr. Stanton who will be assisted in this work, as well as in the course in histology, by Dr. Donald Boyd.

In connection with the course in pathology the most serious need is some arrangement by which post-mortem examinations may be made before the entire class. At present, this instruction can be given only to small sections at irregular intervals. It would appear possible, by combined action of the Albany Hospital, the faculty of the Medical School and the trustees of the laboratory, to arrange for proper facilities at the Albany Hospital. I respectfully suggest to the trustees the necessity of immediate action upon this question.

Of those who have availed themselves of the opportunity to work in the laboratory for considerable periods of time are Dr. Ellice McDonald, of Philadelphia; Mr. Leon K. Baldauf, of the Johns Hopkins Medical School; Dr. J. F. Rooney, Dr. E. F. Sibley and Dr. Donald Boyd, of Albany; Mr. Joseph L. Donhauser, Mr. Erastus Corning, Mr. C. W. H. Hacker and Mr. T. A. Hull, of the Albany Medical School; Mr. Jerome Meyers, of Dartmouth College; and Mr. W. E. Wright, of Liberty, N. Y. These gentlemen have assisted in the routine work of the laboratory, pursued special lines of study, or engaged in research work. To Dr. Ellice McDonald, we are especially grateful for valuable assistance during the first half of the year.

For the year 1904-'05 Dr. E. F. Sibley has agreed to serve as voluntary assistant in all laboratory work.

Original investigations in various lines of work have been carried out during the year. The expense of the experimental investigations has been defrayed by a grant from the Rockefeller Institute for Medical Research; a similar grant has been obtained for the year 1904-'05. The following papers have been published or are now in press:

1. Pearce, R. M., Concerning the Specificity of the Somatogenic Cytotoxins.
   (Conducted under a grant from the Rockefeller Institute for Medical Research).
   Journal of Medical Research, 1904, xxi, 1; also Albany Medical Annals, 1904, xxv, 576.

2. **Pearce, R. M.**, The Experimental Production of Liver Necroses by Haemagglutinins, (*in press*).
   (Conducted under a grant from the Rockefeller Institute for Medical Research).

3. **Pearce, R. M.**, and **Winne, C. K., Jr.**, Concerning Haemagglutinins of Bacterial Origin and their Relation to Hyaline Thrombi and Liver Necroses, (*in press*).
   (Conducted under a grant from the Rockefeller Institute for Medical Research).

4. **Pearce, R. M.**, The Islands of Langerhans in Congenital Syphilitic Pancreatitis.
   American Medicine, 1903; vi, 1020; also, Albany Medical Annals, 1904, xxv. 88.

5. **Pearce, R. M.**, The Pathology of Diabetes.
   Albany Medical Annals, 1904, xxv, 329.

6. **Pearce, R. M.**, Experimental Pancreatitis Considered in its Relation to Acute Lesions of the Pancreas in Man.
   American Medicine, 1904, vii, 853; also Albany Medical Annals, 1904, xxv, 389.

7. **Pearce, R. M.**, Cancer of the Pancreas and Glycosuria; A Histological Study of the Islands of Langerhans, (*in press*).

8. **McDonald, E.**, Complications and Degenerations of Uterine Fibromyomata.
   Journal of the American Medical Association, 1904, xlii, 1344; also, Albany Medical Annals, 1904, xxv, 515.

9. **Carey, H. W.**, and **Laird, A. T.**, A Peculiar Hypertrophy of the Prostate Accompanied by an Ascending Infection and Cysts in the Ureters, with a General Discussion of Ureteritis Cystica.
   Albany Medical Annals, 1904, xxv, 532.

10. **Stanton, E. MacD.**, and **Shaw, H. L. K.**, Infantile Inguinal Hernia of the Vermiform Appendix with Adhesion to the Epididymis.
   Albany Medical Annals, 1904, xxv, 589.

11. **Lipes, H. J.**, A Study of the Changes Occurring in the Endometrium during the Menstrual Cycle.
   Albany Medical Annals, 1904, xxv, 94.

Other investigations not yet completed are: An Experimental Study of Hydrophobia, by Dr. E. MacD. Stanton; A Study of the Uric Acid Elimination in Gout, by Dr. A. T. Laird; Cancer of the Appendix, by Mr. Leon K. Baldauf; and An Investigation of the Giant Cells occurring in the Musculature of the Pregnant Uterus, by Mr. Erastus Corning.

In pursuance of a plan already submitted to you it is my intention to prepare for general distribution a volume which will contain the above papers. This volume will be known as "Studies from the Bender Laboratory," and with your financial support, I hope to make it an annual publication.

Improvements and Repairs—These have not been extensive. The need, however, of more space for the general work of the laboratory led me to convert the large room on the first floor, formerly occupied by the janitor, into an office for the stenographer and the proper storing of the laboratory records. The janitor has been given the room on the third floor, formerly a cloak room for the use of students. The latter have been provided for by placing hooks in the large hall off the class room of this floor. Three small private rooms intended for the use of persons conducting special researches have been procured by partitions isolating the unused portion of the large class room on the third floor. These assure more or less privacy and add to the desk space available for special work. Other improvements include an additional work table in the director's room, a work bench in the basement with vise and tools for the janitor's department, important changes in the arrangement of the animal room and additional shelving in various parts of the building. During the past summer all the floors have been filled and oiled, the wood work of halls and lecture room varnished, the walls of halls and office painted, and various repairs to the windows made. To prevent a repetition of the disastrous flooding of the basement which occurred during the freshets of last spring, the ground at the rear of the building has been raised and sodded and the walls and cover of the cellarway repaired. The appearance of the front of the building has been improved by cleaning the brick work and repointing the stone work and steps.

Gifts—A portrait of Mr. Matthew W. Bender, presented by Dr. George E. Gorham, has been placed in the lower hall; a series of fifty-one portraits, the gift of Dr. George Blumer, representing prominent workers in scientific medicine, in the large class room of the third floor; and a portrait of Dr. George Blumer, in the Director's room.

RICHARD M. PEARCE.

Reprinted from **Albany Medical Annals**, August, 1904.

CONCERNING THE SPECIFICITY OF THE SOMATOGENIC CYTOTOXINS.*

Presented at the Fourth Annual Meeting of the American Association of Pathologists and Bacteriologists, held at New York, April 1st and 2nd, 1904.

By RICHARD M. PEARCE, M. D.,
Director of the Bender Laboratory, Albany, N. Y.

CONTENTS

Introduction—Methods—Observation of immunized animals—On the action of anti-sera obtained by the injection of (*a*) red blood cells, (*b*) liver, pancreas, adrenal and kidney containing blood, (*c*) the same organs free of blood, (*d*) blood serum, (*e*) urine, and (*f*) bile—Controls with normal serum—Relative toxicity of the various sera—Summary and Conclusions—References.

INTRODUCTION

This study was undertaken with the object of demonstrating, by a comparative study of the somatogenic cytotoxins, that the action of any given cytotoxin depends on the chemical (receptor) organization of the cell and not upon morphological characteristics; that an artificial anti-serum may have a definite toxic action on several types of cells of widely differing morphology but presumably having in part at least common receptors; that specificity in the sense of morphological affinity is of secondary importance and in the case of some sera may not exist; that many of the results supposed to be due to the specific action of one cytotoxin

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* This study has been conducted under a grant from the Rockefeller Institute for Medical Research.

are due rather to other cytotoxins adventitiously elaborated as the result of improper methods of immunization.

My attention was first attracted to these various phases of cytotoxic activity by some observations made in the course of an experimental investigation of nephrotoxins.* I found that by the usual method of immunization, that is, the injection of the kidney with its contained blood, a serum strongly haemagglutinative and haemolytic was produced and that the haemoglobinuria resulting from the injection of this serum entirely obscured any nephrolytic action it might possess. The haemagglutinative element of the serum also caused the agglutination of the red blood corpuscles; the thrombi thus formed occluding the vessels of the liver with resulting focal necroses of that organ. It was therefore evident that many of the results previously reported as due to a specific nephrotoxin or hepatotoxin were due to haemagglutinins or haemolysins forming in animals improperly immunized. To obviate this difficulty blood-free kidney was used in the immunization with the surprising result that although the serum thus obtained was powerfully nephrotoxic, it was also, in a moderate degree, haemagglutinative and haemolytic. It did not however cause haemoglobinuria. Moreover hepatotoxin, so-called, prepared in like manner possessed similar characteristics but exerted no special action upon the liver.

At this time an extended investigation of the literature indicated that immunization with "washed" or blood free organs had in no instance been practiced. It was evident therefore that a study of cytotoxins by this method of immunization might yield results differing widely from those of previous investigations and possibly of fundamental importance in connection with the question of the specificity of these substances. Before taking up the detailed discussion of this work, it may be well to summarize the more important communications upon the question of specificity.

In the vast amount of literature which has accumulated the

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*Pearce. An Experimental Study of Nephrotoxins, *Univ. of Penna. Med. Bulletin*, 1903, xvi, 217.

predominating feature is the effort to demonstrate a morphological affinity. This is especially evident in the early work which neglects to a great extent the question of chemical (or receptorial) structure. Due consideration has not been given to the very clear and definite statements of Ehrlich and Morgenroth concerning specificity. v. Dungern and Mexter produced anti-sera for ciliated epithelium and testicular cells and found them to be also haemolytic. On account of these results they denied a strict specificity to the cytotoxins. Metchnikoff and Metalnikoff, on the other hand, believing in this specificity, endeavored to explain the double action on the supposition that sufficient red blood corpuscles were injected with the epithelial cells to produce an haemolysin.

Of wider interest is the production of haemolysins by injecting body fluids entirely free of red corpuscles. v. Dungern, Besredka, Tschistovitsch, Müller and Morgenroth by injecting blood serum, and Shattenfroh, Buffer and Crendiropoulo by injecting urine have obtained such. v. Dungern produced an haemolysin also by injecting cow's milk, and recently Portis has obtained a like result by injecting the "colloid matter" of the thyroid. These observations, at first glance opposed to the theory of specificity if considered from the point of view of morphology, are explained by Morgenroth by the presence of free receptors in the blood and urine. These free receptors, as first announced by Ehrlich, appear in these fluids, especially the blood, as the result of the cell changes accompanying normal metabolism. Thus it is possible for receptors of all cells of the body to be present in the blood serum. Naturally, immunization with fluids containing these receptors would result in the formation of specific anti-bodies. Morgenroth therefore draws the conclusion that specificity is a matter not of cells but of receptors, whence a given cell may be in chemical conformity with cells of a different organ or perhaps animal. Recent investigations of anti-thyroid serum (Yates, MacCallum, and Portis) and of anti-adrenal serum (Abbott, Yates) indicate that these have little or no specific action. Unwashed adrenal serum, however, Abbott found to be possessed of a definite haemolytic power; Portis found the same to be true of washed thyroid serum.

In order to study this much debated question of specificity in a somewhat comprehensive manner a comparative investigation of several cytotoxins, as outlined in the introductory summary, was undertaken.

METHODS

The animals selected for this study were the dog and the rabbit; the latter being immunized with the cells and fluids of the former. The method of immunization adopted was that followed in the work on nephrotoxins. All injections were made into the peritoneal cavity at intervals of a week or ten days, the animal being bled a like period after the third, fourth or fifth injection. Preliminary bleedings were made from the jugular veins; the final bleeding from the carotid arteries. The serum thus obtained was injected into the saphenous, occasionally the femoral vein of the dog. In determining the specific effect of these various sera, systematic examinations of the urine and detailed gross and histological studies of the several organs have been made; their action upon red blood corpuscles has been determined *in vitro*. Attempts were also made to determine by the test-tube method the action of the various sera upon emulsions of the several types of parenchymatous cells; but the results were so confusing and contradictory that this method was early discarded in favor of intravenous injection. This method, analogous to pharmacological methods, of testing the action of a serum by its effect on the living cells is, I believe, the only method free of error. Moreover, it is by this method alone that the cytotoxins may be utilized to explain various pathological processes, for while tests *in vitro* may establish the theoretical principles of this method of investigation, substantial progress depends on the experimental application to the living cell in its normal environment.

Some information concerning what may be called the more general action of a serum has been determined by observing fluctuations in body weight; and of the relative lethal action, by a comparative study of dosage.

The histological methods include hardening in Zenkers, Müller's and Fleming's solutions; imbedding in celloidin and paraffin; and staining by haemotaxylin and eosin, methylen blue and eosin, Mallory's connective tissue stain and saffranin. The various fresh methods have been utilized in the study of fatty and pigmentary changes.

OBSERVATIONS OF IMMUNIZED ANIMALS

Contrary to general opinion the rabbit may readily be treated with various animal cells and fluids if due attention is paid to cleanliness and to the condition of the animal as shown by fluctuations in body weight. In this series the only deaths occurred among rabbits receiving bile and unwashed liver. Fifty per cent. of the animals treated with these substances succumbed before the third injection. This result is apparently due to the toxicity of bile, for no difficulty was encountered in animals receiving washed liver, blood corpuscles or blood serum. The kidneys of animals dying within a few days after the injection of bile exhibit a well marked degeneration of the convoluted tubules with deposition of a yellowish pigment.

Necrosis and suppuration of the subcutaneous tissues may occasionally occur after the injection of organ emulsions; while encapsulated masses of the injected material in the peritoneal cavity are not infrequent. In one instance after injection of pancreas emulsions fat necroses of the mesenteric, perirenal and pelvic fat were observed.

The changes in the urine are but slight; a heightening of color may occur not uncommonly after injections of blood and adrenal; slight traces of albumen are infrequently found; glycosuria, transitory and of slight degree usually follows the injection of adrenal.

The several organs of these various animals with the exception of those receiving bile, exhibited no histological changes of any moment.

ACTION OF SERUM RESULTING FROM THE INJECTION OF ERYTHROCYTES

While the action of haemolytic sera *in vitro* is well known, little attention has been paid to the changes resulting from its injection into the living animal. Kraus and Fukuhara only, as far as I am aware, have described the histological changes. As such observations are essential, as controls to the experiments to follow, I have made a careful study of this phase of the subject. Rabbits were immunized with defibrinated and washed blood respectively, receiving three to five doses of five centimetres each. Whether defibrinated blood or washed corpuscles are used appears to make no difference in the potency of the serum. Seventeen dogs have received this serum, intravenously, in doses varying from 1:3000 to 1:450.* The effect varied with the dosage. In large amounts (1:600 to 1:400) death usually occurs in from three to fifteen hours. Post-mortem examination of dogs poisoned in this way show the blood to be laked and soft gelatinous clots to be present in the heart and large vessels. The internal organs especially the liver, are intensely congested; the serous cavities may contain a small amount of blood tinged fluid. If the bladder contains urine it is dark claret colored, rich in albumen with a sediment composed of casts, coalesced masses of altered haemoglobin and granular and fatty renal cells. Histological examination reveals agglutinated red blood corpuscles in the various organs; the vessels of the spleen and liver are intensely congested, the cells of the latter often being compressed and disorganized; beginning necrosis of liver cells is not infrequent. The kidney tubules present a wide-spread fatty metamorphosis; their lumina contain altered haemoglobin in the form of casts or irregular granular material; the tissue spaces are oedematous and an accumulation of coagulated serum may be seen in the glomerular spaces.

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* This method of indicating the dose refers to the relation between the amount of serum injected and the weight of the animal. Thus 1:525 indicates that a dog weighing 6300 grammes received 12 c. c. of serum or 1 c. c. to 525 grammes of body weight.

The smaller doses of 1 :1000 to 1 :700 are usually not fatal; but the dogs develop within eighteen to twenty-four hours a haemoglobinuria which persists for three to five days. After the disappearance of the haemoglobin the urine is still high colored and deeply stained with bile. A yellow jaundiced condition of the conjunctivae is a constant symptom. The albuminuria which accompanies the acute condition rapidly diminishes as the urine becomes clear of blood pigment although it may be detected by the heat test for many days; in one animal persisting for three weeks. The urinary sediment contains the products of the destruction of red blood corpuscles and usually many renal cells. Beginning with the second or third day a few casts of the finely granular type are found, but not invariably. Hyaline liver necroses* due to agglutinated red blood corpuscle thrombi are constantly present in these animals. Equally constant is a fatty degeneration of the kidney, which is most marked in the tubules of the medullary rays. Hemorrhages into the adrenal occurred in two of the seventeen animals. They were also found occasionally in the lung.

With doses as low as 1 :1200 to 1 :3000 haemoglobinuria does not always result, but the urine is bile stained and contains albumen. Changes similar to those described above but less marked may occur in the liver and kidney.

The attempts to produce haemolytic sera with small amounts of blood have been of great interest. These were undertaken for the purpose of controlling sera prepared by injecting organs (adrenal) which contain an amount of blood so small that it has heretofore been considered negligible. A series of rabbits receiving 0.1 cubic centimetre of defibrinated blood yielded, after the second injection, a serum which was moderately agglutinative and haemolytic *in*

*** This condition has been the subject of especial investigation and will be considered in detail in another communication.**

vitro; after five injections the serum was immediately and powerfully agglutinative and haemolytic. This serum injected into dogs in doses of 1:550 to 1:345 causes haemoglobinuria, multiple liver necroses, fatty degeneration of the kidney and other changes, including adrenal haemorrhages, similar to those produced by sera prepared from larger amounts of blood. One dog, receiving a dose of 1:350, died in four hours with evidence of extensive thrombosis due to agglutinated red blood corpuscles.

SERUM FROM UNWASHED ORGANS (KIDNEY, LIVER, PANCREAS AND ADRENAL)

In this series the serum was prepared in the usual manner by injecting emulsions of the unwashed organ, that is, with the normal post-mortem blood content. Four to twelve grammes were used at each injection of kidney, liver and pancreas; while animals immunized against adrenal cells received a pair of the organs at each injection. The experience of Yates in the production of adrenal serum indicates that a larger amount of adrenal tissue has no appreciable effect on the character of the serum.

All these sera, naturally, contain haemagglutinin and haemolysin. The liver, kidney and adrenal sera injected into the dog in doses of 1:900 to 1:300 produce similar changes which, moreover, cannot be distinguished from those due to a pure haemolytic serum. Haemoglobinuria, liver necroses, fatty degeneration of the kidney and deposition of blood pigment in spleen and lymph nodes are constant. Only in the case of the kidney serum was a dual action evident. Here, the persistence of albumen and a larger number of casts (granular, epithelial and fatty) after the disappearance of the haemoglobinuria indicated the action of the specific nephrotoxic constituent. This serum saturated with washed red blood corpuscles at zero temperature lost all but a trace of its haemolytic power but was still powerfully nephrotoxic.

No changes occurred in the liver or adrenal which could be ascribed to their supposedly specific sera. The kidney serum in one instance produced focal hemorrhages in the adrenal; the adrenal serum similar lesions in the lung.

The pancreas serum in doses of 1 :800 to 1 :390 did not produce haemoglobinuria but a persistent albuminuria with fatty degeneration of the kidney. The strongest dose given (1 :390) caused also well marked focal necroses of the liver with evidence of red blood cell thrombosis. No change in the pancreas cells could be demonstrated.

Of these four sera that prepared from adrenal appears to be the most toxic, causing death in less than twenty-four hours in dose of 1 :400.

It will be seen from this summary that these sera, with the possible exception of nephrotoxin, produce lesions which differ in no way from those due to a serum prepared from erythrocytes and that they may all readily be explained by the action of haemagglutinin or haemolysin.

SERA PREPARED FROM WASHED ORGANS (KIDNEY, LIVER, PANCREAS AND ADRENAL)

In this series the blood, lymph and the various secretions with their free receptors were removed from the organs by prolonged washing with warm, sterile salt solution. After this procedure it was assumed that only the cells with their fixed receptors remained. The kidney was readily washed through its arteries; the adrenal, pancreas and liver at one time through the abdominal aorta; the clearing of the liver vessels was augumented by washing also through the portal vein. The success of this procedure was tested by immediate examination of the respective organ emulsions and later by examination of hardened sections of the organs. Kidney, adrenal and pancreas, absolutely blood free, were readily obtained; a very few red cells (one or two in three or four fields) were always found in the liver emulsions, despite the most thorough washings with fifteen to twenty litres of salt solution. These cells, however, appear to have had little influence upon the character of the serum produced.

All sera resulting from the injection of these blood free emulsions have the power of agglutinating and haemolysing red blood corpuscles *in vitro.* The agglutination in all instances is immediate and powerful. The haemolytic activity of the adrenal serum is almost equal to that of serum prepared from red blood corpuscles; liver, pancreas and kidney sera are less powerful, their relative strength being in the order named. None of these sera on the other hand are sufficiently powerful to produce haemoglobinuria when injected into the circulation of the dog. My experience is different from that of Portis, who has recently described a serum prepared from washed thyroid, which is haemolytic *in vitro* and in animals produces haemoglobinuria.

The only one of these sera which has a definite action in the sense of morphological specificity is nephrotoxin. The action of this cytotoxin I have recently described in detail, and only a general summary is now necessary. Doses of 1:1600 to 1:500 produce severe albuminuria and cast excretion. The casts are finely granular, and less frequently fatty, epithelial and hyaline; granular and fatty renal cells are usually abundant. The albumen gradually diminishes in amount, but may persist in faint traces for two weeks or more; the casts usually disappear within twelve to fifteen days. The kidney is swollen and oedematous with slightly adherent capsule. On section the cortex is oedematous and pale yellow in color with occasionally a few punctate haemorrhages; the glomeruli are distinct but pale. Histologically the cells of the convoluted tubules are found to be swollen and granular; the cells of the tubules in the medullary rays are vacuolated and osmic acid preparations reveal extensive fatty metamorphosis; the tubules especially those of the pyramids contain much granular material and many casts. Exudation into the glomerular space and hyaline thrombosis with degeneration of the glomerular tuft may occur. With the exception of the liver, which in some animals exhibited extensive granular degeneration no other organs appear to be affected by this serum.

The action of the so-called hepatotoxin is variable. In doses of

1 :1000 to 1 :525 its chief action is to cause a more or less extensive fatty metamorphosis of the kidney. This may or may not be accompanied by albuminuria; in two experiments the albuminuria was equal to that resulting from the administration of nephrotoxin and abundant excretion of casts was present. That definite changes are produced in the liver by this serum is not easily determined. The only change observed was an increased granulation of the liver cells with occasionally slight fatty transformation. This appearance however does not differ from that frequently seen in the liver of apparently normal dogs and is quite constant after the administration of other anti-sera, especially adrenal serum. Focal necroses of the liver due to this serum I have seen in but one instance. These were few in number and followed the administration of a powerful dose (1 :266) of a strongly haemagglutinative serum. As agglutinated masses of red blood corpuscles could be seen in the vessels of the necrotic areas, I consider this action to be due to the agglutinin present and not to a hepatotoxic constitutent of the serum. The necroses described by Delezenne and others working with serum prepared from the unwashed organ may, I believe, be explained in like manner. The changes in the urine described by Delezenne I have not seen.

Adrenal serum in doses of 1 :700 to 1 :550 produces no lesion of the adrenal gland; but well marked granular and fatty transformation of liver and kidney. One animal, killed forty-eight hours after a dose of 1 :556, presented multiple minute haemorrhages of the lungs and liver with free haemorrhages into the glomerular spaces of the kidney. A peculiar phenomenon observed in all animals receiving adrenal serum was an immediate blanching of the mucous membranes with cardiac and respiratory disturbance. This condition, which lasted fifteen to twenty minutes and necessitated the employment of artificial respiration, was not observed in animals receiving other cytotoxic sera. Unfortunately a kymographic study of this condition was not made.

Washed pancreas serum produces in doses as high as 1:620 no recognizable changes in the pancreas and but moderate granular and fatty metamorphosis of the liver and kidney. The transitory glycosuria described by Surmont and by Carnot and Garnier I have not seen. Their injections were made, however, directly into the pancreas; the glycosuria therefore may have been the result of trauma and analogous to that observed by Flexner and Pearce to follow various injuries to the pancreas.

SERA PREPARED BY INJECTING BLOOD SERUM, BILE AND URINE

As has been stated above, several investigators have produced haemolytic sera by immunizing animals with blood serum, urine and other fluids free of red blood corpuscles. This result Morgenroth explains is due to the presence of free receptors normally constitutents of the body fluids. In order to determine if sera thus prepared contain cytotoxins for cells other than red blood corpuscles; also to control other experiments of this series, I have injected rabbits three to five times with the blood serum, bile and urine of the dog in doses of five to ten cubic centimetres.

All three sera thus prepared are strongly haemagglutinative. The serum produced by injecting urine is powerfully haemolytic, that by injecting serum, moderately haemolytic, while the "anti-bile" serum has no haemolytic power whatever. This peculiarity of "anti-bile" serum has been observed recently by Ruffer and Crendiropoulo, and is apparently to be explained by the production of anti-haemolysin, the bile being naturally haemolytic.

"Anti-bile" serum in doses of 1:620 and 1:700 causes fatty degeneration of the kidney and focal necroses of the liver. These latter are accompanied by agglutinative red-blood corpuscle thrombosis and apparently due to a mechanical disturbance of the liver circulation. No changes are found in other organs.

The serum of rabbits receiving dog's serum injected in doses of 1:1000 to 1:390 causes extensive fatty degeneration of the kidney with sometimes slight traces of albumen in the urine.

The serum of rabbits receiving dog's urine produces in the dog a distinct congestion of the liver; otherwise no appreciable changes of either tissues or excretions follow doses as high as 1 :674.

CONTROLS WITH NORMAL RABBIT'S SERUM

Normal rabbit's serum injected in doses of 1 :1320, 1 :900, 1 :600, 1 :500 and 1 :300 was without influence on the urine or histological structure of the various organs examined (kidney, liver, pancreas and adrenal).

RELATIVE TOXICITY OF THE VARIOUS SERA

An attempt has been made in addition to the above described methods of study to gain some idea of the relative toxicity of the various sera by a comparison of the changes in body weight and of the varying periods of time elapsing before fatal termination. Little information has been obtained by the study of changes in weight, for while a loss of weight is more or less constant, there is little variation according to the kind of serum injected, except that an appreciably greater loss of weight occurs in animals receiving sera which produce albuminuria (nephrotoxin) and haemoglobinuria (haemolysins produced by defibrinated blood and unwashed organs).

Death followed only after the use of sera prepared from red blood corpuscles and from blood containing organs. With the exception of the powerful nephrotoxin, prepared from washed kidney cortex, described in a previous communication,* death has never resulted from the injection of sera prepared from washed parenchymatous cells or from blood-free body fluids. There is apparently considerable difference in the toxicity of the haemolysin produced by the injection of red corpuscles and those produced by washed parenchymatous cells; washed adrenal serum, for example, the haemolytic power of which *in vitro* is almost as great as that of true haemolysin has never caused death. On the other hand, it is of interest that the lethal power of a serum produced by blood injected in 0.1 cubic centimetre doses is almost as great as that following the injection of five cubic centimetre doses The former has caused death in four hours, in dose of 1 :350; the latter in three hours, in dose of 1 :450. With these sera may be compared the unwashed adrenal serum which caused death in less than twenty-four hours in dose of 1 :400. These results indicate that as a general rule the power of a serum is not increased by large immunizing doses.

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* *Loc cit.*, page 228.

SUMMARY AND CONCLUSIONS

From these experiments it is evident that the cells of the various organs of the body while differing in morphology and function have certain receptor characteristics in common and that one type of cell may therefore produce anti-bodies affecting several cells of differing morphology but with like receptor groups. This is shown by the sera prepared from washed liver, kidney, pancreas and adrenal, all of which agglutinate and haemolyse red blood corpuscles, and may cause degenerative changes also in the liver and kidney. Some of these cytotoxic sera have no effect upon organs for which they are supposed to have a morphological affinity, but exert a powerful lytic influence upon other cells. Aside from nephrotoxin, which has a distinct injurious action upon renal epithelium the various cytotoxins studied have no specific action in the morphological sense. The action of the kidney serum itself cannot be said to be specific, for in addition to the nephrotoxic element another constitutent (haemolysin) is present. The action of this serum might perhaps be described as "special." Pancreas and adrenal serum on the other hand are devoid even of special action, while the lesions of so-called hepatotoxin are doubtful and may be produced by other sera. The striking characteristic of adrenal serum is its powerful haemolysin.

The presence of free receptors in the various body fluids is shown by the appearance of anti-bodies in the serum of animals receiving serum, bile and urine; the diverse character of these receptors by the variety of cytotoxins thus formed. These observations offer strong support of the view that specificity is a function of receptors and not of cells.

A comparison of the results obtained by sera prepared from washed organs with those of sera prepared from blood and blood containing organs indicates that many of the positive results described as specific and characteristic of the action of certain cytotoxins are due rather to haemagglutinin and haemolysin adventitiously formed as the result of impure methods of immunization.

In connection with the activity of haemolysin it is also necessary to differentiate sharply between the primary specific action upon the red blood cells and the secondary action upon other cells, as those of the kidney, due to the toxic effect of haemoglobin derivatives and possibly other substances set free by the destruction of the red blood cells.

Another phase of the question, heretofore entirely disregarded, is the part played by haemagglutinin. This substance was present in all the sera studied, and in some, when sufficiently powerful, caused the formation of red blood corpuscle thrombi and a resulting mechanical disturbance of the circulation leading to degeneration, necrosis and haemorrhage. This action is best illustrated by "anti-bile" serum which is without haemolytic power, but through its powerful agglutinin causes the formation of red blood corpuscle thrombi and thus the production of widespread liver necrosis. Such lesions have heretofore been confounded with the action of the cytolytic constituent of a serum, and have been considered specific while they are in truth due to the much simpler agglutinating body.

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THE EXPERIMENTAL PRODUCTION OF LIVER NECROSES BY THE INTRAVENOUS INJECTION OF HAEMAGGLUTININS.*

Presented before the American Association of Pathologists and Bacteriologists at the fourth annual meeting held in New York, April 1 and 2, 1904.

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Introduction—This investigation was undertaken with the object of demonstrating experimentally that red blood corpuscles through the agency of agglutinins become fused together and form thrombi which occluding the vessels of the liver may lead to hyaline necrosis of liver cells. That these lesions might thus be produced, was indicated by observations made during a study of various cytolytic sera. In the course of an experimental study of nephrotoxins,[1] it was noted that focal necrotic lesions of the liver with associated hyaline thrombi frequently followed the intravenous injection of sera possessing considerable hæmagglutinative power, but did not follow the injection of sera devoid of this characteristic. Flexner's[2] communication concerning agglutinated red blood corpuscle thrombi, which had appeared but a short time before, suggested the possibility of these hyaline thrombi being composed of red blood corpuscles. A careful study of the lesions proved this to be the case, and a series of experiments was therefore at once begun for the purpose of establishing definitely the power of agglutinin to produce red cell thrombi and also to establish a relation between the thrombi and the necrotic lesions. Later, my interest in the subject was stimulated by the appearance of Boxmeyer's[3] work on the liver necrosis of hog cholera. Boxmeyer found that while one type

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* This investigation was conducted under a grant from the Rockefeller Institute for Medical Research.

[1] PEARCE. An Experimental Study of the Nephrotoxins, *University of Penn. Med. Bull.* 1903, xvi, 217.

[2] FLEXNER. *University of Penn. Med. Bull.*, 1902, xv, 324.

[3] BOXMEYER. *Journal of Medical Research*, 1903, ix, 146.

of lesion was due to a plugging of the capillaries by endothelial cells, aided probably also by a direct action of the toxins upon the liver cells, another type could be explained only by the occlusion of capillaries by fused masses of red blood corpuscles (hyaline thrombi). Although he believed the fusion of these cells to be due to an agglutinin, he made no tests to demonstrate its presence.

As far as I am aware no efforts have heretofore been made to demonstrate experimentally a relation between agglutinins and liver necroses. Focal necrotic lesions of the liver following the injection of cytotoxic sera have been described by Delezenne,[4] Kraus[5] and Fukuhara,[6] but in no instance has it been suggested that agglutinins were concerned in their production.

Methods—Hæmagglutinative sera have been prepared by injecting the rabbit with various organs and fluids of the dog. As the investigation was carried on simultaneously with another which had for its object the determination of the relative specificity of the somatogenic cytotoxins,[7] it has been possible to work with a large number of artificial sera. These include sera prepared by injecting defibrinated blood, washed blood corpuscles, blood serum, bile, urine and washed and unwashed liver, pancreas, kidney and adrenal. All these sera possess the power of agglutinating the red blood corpuscles of the dog in vitro; all, however, as will be seen are not sufficiently powerful to cause red blood corpuscle thrombi in the living animal. The sera was injected under ether anæsthesia, into the saphenous vein of the dog, and after varying periods of time the animals were killed by chloroform. The histological methods of examination include hardening in Zenker's, Müller's and Fleming's solutions; imbedding in celloidin and paraffin; and staining by hæmatoxylin and eosin, methylen blue and eosin, Mallory's connective tissue stain, Weigert's fibrin stain and safranin.

General Summary of Results—Liver necroses were readily produced by sera obtained by injecting bile, blood and blood containing organs; they did not occur after the use of sera prepared by injecting urine, serum and washed organs, except in one instance in which an exceedingly high dose of washed liver serum was administered. The power of these several sera to produce conglutinative thrombi and consequently necroses varies naturally according to the degree of agglutinating activity which they possess. While the most potent sera judging by the reaction in vitro and by the extent and severity of the lesions produced, are those prepared by injecting blood and organs containing a large amount of blood, as the liver and kidney, it is worthy of note that the agglutinative power does not depend entirely on this element, for sera almost as powerful were obtained by injecting bile which contains at best only blood derivatives. On the other hand the various sera prepared by injecting blood free fluids and organs as urine, serum and washed organs, while without power to cause sufficient agglutination in the animal body to bring about the formation of conglutinative thrombi, do cause distinct agglutination *in vitro*. The production of hæmagglutinins therefore would appear to depend on the same principles which govern the production of cytotoxins; that is, upon the similarity in part at least, of the receptor (chemical) composition of the various cells and fluids.[8]

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[4] Delezenne. *C. R. de l' Acad. des Sciences*, 1900, cxxxi, 427, cited by Sach, *Biochem., Centralb.*, 1903, i, 616.

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[6] Fukuhara. *Ziegler's Beiträge*, 1904, xxxv, 434.

[7] Pearce. Concerning the Specificity of the Somatogenic Cytotoxins, *Jour. of Med. Research*, 1904, xii, 1.

The more powerful sera produce multiple liver lesions almost uniformly when administered in doses of 1:1000 to 1:500;[9] smaller doses (less than 1:1000) may produce necroses, but are usually without effect; large doses (1:500 to 1:300) usually cause death within a few hours. This last result, however, has occurred only with the use of sera produced by injecting blood and unwashed adrenal. In this regard it is of interest that the serum of an animal receiving blood in doses of 0.1 cubic centimeter is as powerful as that of animals receiving doses of five cubic centimeters. The serum of animals receiving washed blood is as potent as that of those receiving defibrinated blood. The power of unwashed adrenal serum to produce liver necroses was but slightly less than that of sera prepared from blood. Unwashed liver and kidney sera and serum prepared by injections of bile caused liver necroses in the same doses as did the above sera, but had no lethal effect. On the other hand, washed liver serum, the only one of this group (sera prepared from washed organs) to cause necroses, did so only when administered in very large doses (1:266), and had no lethal action. Heated sera suffered no loss of agglutinating power.

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[8] For a consideration of this subject and also for a description of the cytolytic action of the various sera here mentioned see Journal of Medical Research 1904, xii, 1. Only the agglutinative action of the sera and the lesions produced in the liver will be considered in this communication.

[9] This method of indicating the dose refers to the relation between the amount of serum injected and the weight of the animal. Thus 1:1000 indicates that an animal weighing 5000 grammes received 5 c. c. of serum or 1 c. c. to 1000 grammes of body weight.

The necroses produced by these various sera develop in from twenty-four to forty-eight hours. They are usually widespread, closely massed and often confluent. The surface of the liver presents a mottled appearance; small, irregular, yellowish brown or greyish yellow non-elevated areas being sharply outlined by the deeply congested normal substance of the liver. When the congestion is intense the necrotic areas appear depressed owing to the swelling of the congested liver surrounding them, and fine points of hæmorrhage may be seen. On section the brownish yellow areas have a distinct hyaline appearance. The distribution of these lesions is almost always superficial, few necroses being found more than half a centimeter below the surface. When the distribution is not so diffuse, the more prominent lesions are at or near the free edges of the lobes and occasionally limited to the smaller lobes about the gall-bladder. All sera produce uniformly the same type of lesion, though not always the same degree of destruction.

Histology—The necrotic lesion involves the greater portion of a lobule, often the adjoining portions of several lobules. Most frequently the necrosis is in the peripheral portion of the lobule, but occasionally the central zone is involved. The relation to the portal vessels is striking, the altered areas frequently entirely surrounding the portal vessels. The necrosis is hyaline in character, the cells stain poorly with eosin, thus being sharply marked off from adjacent unaltered cells. The nuclei may be fragmented, but more commonly are shrunken and irregular, and often fail entirely to take the stain. Leucocytic infiltration seldom occurs. The capillaries in the midst of these areas are tightly packed with red blood corpuscles. In some capillaries the cells are loosely arranged, but in others homogeneous more or less cylindrical cast-like masses of coalesced cells are seen. The endothelium of the capillaries is usually unaltered and accumulations of endothelial cells do not occur. An occasional endothelial cell or polymorphonuclear leucocyte may be found in the midst of these masses, but are never present in considerable numbers. In the smaller portal veins adjacent to the necrotic areas larger ovoid or coalesced masses are seen. These may entirely fill the vessel, though usually a few loose red cells may be found at the periphery. The appearance of these masses is not constant. All contain granular and hyaline areas; in the majority the centre is granular and the periphery hyaline, but frequently this arrangement is reversed. In some, the transition from normal corpuscles to irregular, distorted or varicose corpuscles and finally to hyaline and granular masses may be seen. The hyaline areas upon close examination may be resolved into a tangled mass of irregular varicose threads, representing apparently greatly distorted and elongated corpuscles. Adherent to the walls of the larger vessels distinctly hyaline masses with stalactite-like processes may occasionally be seen. These are apparently of the same origin as the smaller thrombi. Fibrin does not enter into the formation of these thrombi, though the detection of finer threads of fibrin is rendered difficult by the tendency of the altered corpuscles, especially after Zenker hardening, to take the fibrin stain. Fibrin threads may occasionally be found at the periphery of the larger thrombi, but I have never seen them in connection with the smaller plugs.

Taking advantage of the fact that an interlobular vein supplies adjacent portions of several lobules, it has been possible, especially in serial sections, to demonstrate a relation between a thrombus of such a vein and necrosis of the peripheral portions of the lobules in direct relation to it. Also in areas of extensive necrosis involving all but the hepatic vein zone of many lobules, the portal terminals were found uniformly occluded. While it is possible for the capillary thrombi within the lobule to cause necroses the more important plugging occurs, I believe, in the perilobular veins or the branches from which they originate. The anatomical relation of the agglutinated corpuscles to the lesion, in the absence of bacteria, phagocytic cell or fibrin thrombi, conclusively indicates that the necroses are due to this obstruction of the smaller veins.

In some animals dying within a few hours after the injection of large amounts of serum (1:400 to 1:500) an extraordinary condition consisting of extreme congestion of the vessels and disorganization of the liver cells was found. Vessels of all sizes were widely dilated and filled with agglutinated corpuscles, while the pressure exerted caused a narrowing of the columns of liver cells with more or less displacement. In one instance the pressure was so great that complete disorganization of the liver substance had occurred. This destruction was so extreme that the histological picture, large sinus-like spaces separated from one another by this compressed and irregularly arranged columns of hepatic cells and filled with closely packed agglutinated and more or less distorted red blood corpuscles, was most suggestive of a cavernous angioma with thin trabeculæ. In this early lesion the liver cells stained poorly, but no distinct necroses were found in animals dying within eighteen hours. The smaller doses, less than 1:1000, on the other hand, never produced changes in the liver other than an occasional slight congestion.

In connection with these lesions the following questions naturally occur. Why do not similar extensive thromboses occur in other organs? Why do necroses occur almost exclusively at the periphery of the liver and why are they limited practically to the portal area? Capillary thrombi do occur in other organs, especially in the glomeruli of the kidney, the periphery of the lung, in the adrenal and in all these locations they may be accompanied by minute hæmorrhages. Their occurrence is, however, infrequent and unaccompanied by necrosis, except possibly in the glomerulus of the kidney. That they do not occur more frequently is probably due to peculiarities in the circulation in the various organs. It is possible that the slow circulation of the portal system allows the formation of larger masses of agglutinated corpuscles than could form in the rapid flow of the other organs; while on the other hand the narrow capillaries of the liver are more readily occluded. The first of these factors would also explain the greater frequency of the lesion in the portal vein area of the lobule. The more frequent involvement of the superficial portions of the liver can only be explained by Boxmeyer's assumption that the blood supply of this portion of the liver is less complete, and the collateral circulation less perfect than in the deeper portions of the liver.

Attempts to Demonstrate the Mechanical Nature of the Thrombosis.—As the sera, with one exception, used in these experiments was hæmolytic, and as several possessed other cytotoxic constituents, it became necessary to rule out the direct action of these cytotoxins upon liver cells and also the possibility of an obstruction of the circulation by the remains of hæmolysed red blood corpuscles. Several observations bear on this point and support the theory of mechanical obstruction by agglutinated corpuscles. In order to definitely determine that an agglutination similar to that seen *in vitro,* takes place in the circulating blood of an animal receiving an agglutinative serum, the blood of a dog was examined four minutes after the injection of serum in the dose of 1:350. Blood taken quickly from the heart, the superior vena cava, and the cut surface of the liver, and diluted with salt solution showed abundant coalesced masses of red blood corpuscles. Upon standing, a light jelly-like clot formed with a supernatant fluid containing distinct agglutinated masses not readily disintegrated by agitation. Microscopically these masses, which varied in size, were seen to be composed of from twenty to seventy or more red corpuscles many of which were distorted or elongated and often so fused together as to be indistinguishable one from the other. In another instance twenty-four hours after injection (dose 1:985), masses of the same character were found in blood from the cut surface of the liver. Here the cells were so fused together that the outlines of individual cells could not be recognized.

That agglutinin alone is the important factor in producing these necroses is shown by experiments with serum prepared by injecting bile. This serum, while powerfully agglutinative, unlike the other sera used, has no hæmolytic power. It causes, however, in doses of 1:700 widespread lesions of the liver similar to those described above. Attempts to render other sera hæmolytically inactive by heating have been unsuccessful. Animals receiving such sera develop hæmoglobinuria and the renal changes which usually follow the administration of a hæmolytic serum, as well as typical liver lesions, the result of the action of the agglutinin.

As a somewhat imperfect test[10] of the mechanical nature of the thrombosis, attempts were made to produce necroses by injecting agglutinated masses of red corpuscles freed of the excess of immune serum by repeated washing. These masses were prepared by agglutinating dog's blood *in vitro,* and washing hastily in several changes of salt solution. Agglutinated masses, thus prepared, injected into the mesenteric vein in doses of five to ten cubic centimeters seldom produce necroses and those which do occur are not of the same type or so numerous as those produced by the injection of agglutinative serum. They represent the type of granular necrosis with nuclear fragmentation rather than the hyaline type and are very few in number. Associated hyaline thrombi were found only occasionally. In all these experiments the spleen contained a very large amount of altered blood pigment, indicative of the fate of the injected cells. I consider the results of these experiments to be of little significance one way or the other, for the injection of five or ten cubic centimeters of agglutinated corpuscles, an amount readily destroyed in the animal, is in no way comparable to the extensive agglutination resulting from the cumulative action of ten to twenty cubic centimeters of agglutinative serum.

Various controls as the injection of defibrinated normal dogs blood, washed hæmolyzed dogs corpuscles, the blood and the clear serum of dogs in which the liver lesions had been produced, and normal rabbits serum have been uniformly negative.

Effect of Repeated Injections.—The severity and extent of the lesions produced by the injection of agglutinative serum suggested the possibility of producing, by repeated injections, conditions analagous to acute yellow atrophy or the more acute forms of cirrhosis. With this object several animals have received serum intravenously at intervals of one to three weeks. Thus far no permanent lesions have been found in animals which have been killed at the end of seven weeks after receiving three injections. Indeed, from a study of the liver necroses in a small number of animals which have been allowed to live more than a few days, there is very distinct evidence that these lesions are completely repaired. The observations upon this phase of the subject are, however, too few to warrant a definite statement at this time.

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[10] This condition of this test is not perfect, for the haemolytic amboceptors of the serum are of course fixed by the red corpuscles.

May Agglutinins be a Factor in the Production of Liver Necroses in Man?—In considering this question it is not necessary to go into the general literature bearing upon the etiology of liver necroses. That these lesions may be produced by the direct action of bacteria (B. tuberculosis, B. pestis, and the pyogenic cocci) is well known. Mallory[11] has shown very conclusively that they may be due also, especially in typhoid fever, to occlusion of the capillaries by clumps of phagocytic endothelial cells with or without associated fibrin coagula. That a strong toxin in the circulating blood may produce the so-called central necroses is also indicated by his investigations. There remain, however, many focal necroses which cannot be satisfactorily explained. Associated with such are frequently found capillary thrombi described as hyaline or fibrinous. It seems probable that these, in view of the facts set forth in this communication, may be agglutinative red blood corpuscle thrombi and the essential element in causing the necroses with which they are associated. Flexner and Boxmeyer working independently came to the conclusion that the so-called hyaline thrombi were composed of fused red blood corpuscles. Flexner found such thrombi in the intestine of typhoid, the stomach of carbolic acid poisoning and in broncho-pneumonia; and in the rabbit produced them experimentally by the injection of agglutinating substances as ricin, ether and dog's serum; Boxmeyer found them in the liver necroses of experimental hog cholera. It is significant that the latter could readily distinguish necroses due to such thrombi from those due to phagocytic cell thrombi. Many of those who have studied hyaline thrombi, state that they are composed of fused and altered red blood corpuscles, but do not explain the mechanism of the fusion. Ziegler's[12] opinion that they are formed largely from the colorless elements of the red blood cells, is of interest in view of our newly acquired knowledge of agglutination and hæmolysis.

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[11] MALLORY. *Journal of Exper. Medicine*, 1898, iii, 611; *Journal of Medical Research*, 1901, vi, 264.

[12] ZIEGLER. *General Pathology*, Eng. Ed., 1899, p. 122.

In attempting to bring agglutinative thrombi into relation with liver necroses in man it is necessary to explain the origin of the agglutinin. The possibility of its development as a bacterial product in the course of infectious diseases, naturally suggests itself. It is well known that a considerable number of bacteria produce hæmolysins, and it has been demonstrated that a few produce also hæmagglutinins. This agglutinating power is possessed also by several poisons not of bacterial origin. In this connection it is significant that most of the conditions in which hyaline thrombi have been described are of bacterial etiology as hog cholera, typhoid fever, bronchopneumonia, diphtheria and infections with the pyogenic cocci; or intoxications as poisoning by ergotin, corrosive sublimate, carbolic acid, ricin and abrin. Of considerable interest in this connection is Flexner's reference to the occurrence of agglutinative thrombi in the liver lesions of eclampsia. The occurrence of hyaline thrombi in the vessels of the rabbit's ear, after freezing, points also to an injury of red cells leading to agglutination.

It seems probable that the application of experimental methods may demonstrate that agglutinins may be formed in various infectious and toxic conditions in sufficient quantity to cause agglutinative (hyaline?) thrombi with the development of liver necroses and possibly other lesions. Experiments, now in progress, with the products of antolyzed bacteria indicate the presence of such a body in sufficient amount to produce agglutinative thrombi.

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CONCERNING HEMAGGLUTININS OF BACTERIAL ORIGIN AND THEIR RELATION TO HYALINE THROMBI AND LIVER NECROSES.*

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Elsewhere, one of us[1] has described the hemagglutinative power of various cytolytic immune sera and the relation of the red blood corpuscle thrombi (hyaline thrombi) resulting from the injection of such sera to focal hyaline necroses of the liver. The distinct character of the liver lesions thus produced, and the fact that they could be explained only by the presence of agglutinated red blood corpuscle thrombi, suggested the possibility that similar lesions occurring in various infectious diseases might be due to the development of hemagglutinins of bacterial origin. In order to test this supposition we have attempted to demonstrate the presence of hemagglutinins in filtrates of bacteria treated in various ways, and, by the injection of the same into animals, to produce agglutinated red blood corpuscle thrombi and associated liver necroses.

It is not our intention to go into the general literature of these subjects, but merely to touch upon those points which relate to infectious conditions. The more important views concerning liver

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*This study has been conducted under a grant from the Rockefeller Institute for Medical Research. Published also in the *American Journal of the Medical Sciences, October, 1904* necroses may be found in the papers of Flexner,[2] Mallory,[3] Boxmeyer[4] and Opie.[5] That the so-called hyaline thrombi may be composed of altered and fused red blood corpuscles we consider to be definitely established. The recent studies of Flexner,[6] Boxmeyer, and Pearce offer conclusive evidence of such origin and support the earlier observations of Klebs[7] and Ziegler.[8] The occurrence of hyaline thrombi in connection with various infectious and toxic conditions has been emphasized by Welch,[9] who, in his summary of the literature, mentions particularly infections with S. pyogenes aureus and B. cholerae suis, and offers a suggestion concerning their origin from red blood corpuscles. In a later discussion[10] of the subject he brings forth the hitherto unpublished observations of Fisher concerning the plugging of small vessels by agglutinated red cells as the result of injecting typhoid bacilli, and calls attention to the evidence in favor of the interpretation of many of the hyaline thrombi as derived from fused red blood corpuscles. Other important observations are those of Flexner, who found similar thrombi in the intestine of typhoid fever, in bronchopneumonia and in experimental diphtheria; and also of Boxmeyer, who could distinguish, in the livers of rabbits dying of experimental hog cholera, between necroses due to endothelial cell thrombi and those due to agglutinated red blood corpuscle thrombi. The hyaline thrombi occurring in various intoxications, due to either organic or inorganic poisons, and in toxic conditions of doubtful origin, as eclampsia, are undoubtedly of similar nature; but as they do not come within the scope of this study, will not be further considered.

Of considerable historical interest in connection with this question of the occurrence of red blood corpuscle thrombi in the course of infectious diseases are the observations of Hueter,[11] made in 1873. As the result of his studies, to which attention has recently been called by Welch,[10] Hueter came to the conclusion that clumping of red blood corpuscles, causing permanent or transient occlusion of capillaries and small vessels ("glöbulose Stase und Embolie") occurred not uncommonly in septic and other fevers. His theory that this phenomenon constituted the underlying basis of fever has never gained acceptance, but the observations are of interest in connection with our recently acquired knowledge of bacterial hemagglutinins. v. Recklinghausen[12] considers this globular stasis of Hueter to be analogous to a condition found in the capillaries after transfusion of alien blood, and which he describes as an "agglutination" of red blood cells.

In planning this investigation it was evident that as necroses of the liver are most frequently associated with infections by the bacillus of typhoid fever and the bacillus of hog cholera, the bulk of the work should be done with these organisms. In order, however, that no opportunity might be lost, the literature dealing with bacterial hemolysins was examined in the hope of finding reference to organisms which produced also hemagglutinins; of twenty-nine such investigations[13] but six[14] refer to the production of hemagglutinins by bacteria. Kraus and Ludwig found that bouillon cultures of S. pyogenes aureus and Vibrio Paris had the power of agglutinating red blood corpuscles *in vitro* in from ten to twenty-four hours at room temperature. The mass which settled at the bottom of the tube was seen upon agitation to be composed of small clumps of red blood corpuscles which could not easily be disintegrated. The agglutinin they considered to be independent of the hemolysin; but, on the other hand, they state that organisms which do not hemolyse also do not agglutinate. Small amounts of the cultures caused agglutination without hemolysis. Volk and Lipschütz, working with staphylolysin and vibriolysin, describe agglutination in connection with incomplete hemolysis of rabbits' blood, but did not observe it with other bloods. Volk, as a result of his observations, comes to the conclusion that agglutination is due not to a specific body, but to non-isotonicity of the fluid. Calamida states that no agglutination precedes the hemolysis caused by bouillon cultures of the chicken-cholera bacillus. Flexner mentions agglutinins of low activity in filtrates of B. pyocyaneus, B. typhosus, and S. pyogenes aureus. Kayser, in his study of colilysin, observed a clumping of red cells in connection with incomplete hemolysis, but not when complete solution occurred. Of greatest interest, however, and very suggestive, is the observation of Eisenberg,[15] who found the blood of an individual with a generalized pyocyaneus infection to be both auto-agglutinative and iso-agglutinative.

As the result of this survey, it seemed advisable to utilize B. pyocyaneus and S. pyogenes aureus in addition to B. typhosus and B. cholerae suis; and these, with B. dysenteriæ and S. pyogenes, constituted the group of organisms finally selected for study.

METHODS. In previous attempts (Reed,[16] Flexner, Mallory, and Boxmeyer) to produce liver necroses by the injection of microorganisms, either the living culture, grown in the ordinary way, or its filtrate has been used. With the use of the former it has been difficult to distinguish between the direct action of the organism and the effect produced by its toxin; with the latter the action of intracellular toxins has been excluded. In our experiments the direct action of the microorganisms has been eliminated by the use of filtered fluids, and an attempt has been made to obtain the intracellular constituents of the bacterial cells by the utilization of methods destined to cause its disintegration. Various writers have described methods by which the bacterial cell is destroyed and its receptors liberated. Of these methods we have tried, with certain modifications, the processes of autolysis described by Conradi,[17] Neisser[18] and Shiga, and Brieger and Mayer.[19] The various organisms have been grown for twenty-four to seventy-two hours on agar in large flat flasks having a surface of twenty by eight centimetres. The growth on several flasks, usually three or four, has then been scraped off, subjected to 55° C. for forty-five minutes, and placed in tubes containing 0.85 per cent. salt solution at a temperature of 37.5° C. for two to three days. In some instances the fluid has stood for longer periods, varying from one to seven weeks. The fluid has then been filtered (Chamberland B. and F.) and injected intravenously into animals after testing its agglutinative power *in vitro*. At various stages of the process suitable controls were made to demonstrate absence of contamination and the efficiency of the filters.

In addition to this method of growing the organism, an attempt was also made to stimulate the production of hemagglutinin by previously growing the organisms in media containing red blood cells. This method was suggested by the theory of "bacteriogenic cytotoxins," advanced by Welch in his Huxley Lecture: "Certain substances of the host of cellular origin, assimilated by the parasites through the possession of haptophore groups with the proper affinities, become anchored to receptors of the parasitic cell, which, if not too much damaged, is thereby simulated to the overproduction of like receptors; these excessive receptors of the parasite, if cast off into the fluids or the cells of the host, then constitute intermediary bodies, etc." The writer further states: "by a similar mechanism it is possible that parasites may be stimulated to the production also of antibodies other than cytotoxins, such as various agglutinins, precipitins, antienzymes—all adjusted against the host."

Assuming that if this hypothesis might apply to organisms growing in living cells or fluids, it might hold also for those grown on cells outside the body, typhoid and hog cholera bacilli have been grown in various blood preparations. These include both defibrinated and washed blood added in various proportions to salt solution, and fresh sterile rabbits' organs. The period of growth in the various blood mixtures varied from twenty-four to seventy-two hours; in some instances inoculations into fresh blood solutions or upon fresh organs being made on each of three successive days. The sterile organs were prepared according to the technique described by Flexner.[20] By these various methods it was hoped that the organism would be stimulated to produce agglutinins and that this power would be retained during the subsequent growth on agar, giving in the finished autolyzed product, a fluid of appreciably augmented agglutinating power. Observations supporting this theory have been made by Marmorek and by Simon, who found that streptococci grown in media composed of leukocytes alone, or with bouillon added, secrete a toxin of considerable power. Simon[21] believes that the streptococcus in order to secrete toxin must meet a certain resistance to its development, and that this resistance is furnished by something in the leukocytes. This explanation, put in the terms of Ehrlich, corresponds to Welch's hypothesis. Our attempts to produce free agglutinin receptors by growing the organisms in blood we consider analogous to Simon's method of producing toxin by growth in leukocytes.*

Another method employed was the growth of an organism in heated rabbit serum. This was suggested by the observation of Besredka,[22] that the streptococcus produces an hemolysin when thus grown.

RESULTS. The tests for agglutination were made by adding nine parts of the various filtrates to one part of blood. Observations were made at room temperature and at 37.5° C. at varying periods up to twenty-four hours. The clumping of red blood corpuscles by bacterial hemagglutinins is of slight degree as compared with that produced by various cytolytic immune sera. The powerful agglutination of the latter is never seen, and for this reason more careful comparison with controls is necessary in order to detect slight differences in reaction. This feeble activity renders it difficult to make definite statements concerning some of the organisms studied. While all (B. typhosus, B. cholerae suis, B. pyocyaneus, B. dysenteriæ, S. pyogenes aureus and S. pyogenes) in the majority of tests, *in vitro,* showed a slight agglutination as compared with controls the effect of filtrates of B. dysenteriæ, B. cholerae suis and B. pyocyaneus was so slight as to be considered doubtful. With other organisms the agglutination was more evident, being most distinct with filtrates of S. pyogenes. Upon microscopic examination (hanging drop) the clumping caused by the streptococcus was always in the form of massive, more or less branching, rouleaux; while with all other cultures an irregular agglutination of a small number of corpuscles was seen. The agglutination due to the streptococcus could be seen after fifteen to twenty minutes, as the corpuscles settled, while with the other organisms it could be seen only upon agitation after a considerable period of time. More definite results were obtained with rabbits' blood than with dogs' blood.

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*Another point in favor of this theory of bacteriogenic antibodies is the observation of Theobald Smith (verbal communication) that recently isolated cultures of the hog-cholera bacillus have a greater power to produce liver necroses than have old cultures. Accepting Boxmeyer's work on the relation of agglutinative red blood corpuscle thrombi to such lesions, the explanation naturally suggested is, that residence in the animal has stimulated the power of the bacillus to produce agglutinin.

Of unusual interest and very suggestive are the agglutination tests with filtrates of typhoid bacilli previously grown in blood suspensions and on fresh sterile organs; though carried out in but a small number of tests, they appear to be confirmatory of Welch's hypothesis mentioned above. These filtrates, especially those of bacilli grown on sterile organs, exhibit an appreciably greater power of agglutination than the filtrates of organisms grown on agar only.

While no effort was made to study especially bacterial hemolysins, it is of interest that the autolytic products of bacteria as here prepared have never caused hemolysis. This result is in harmony with the observations of Jordan,[23] Williamson[24] and others who hold that the hemolysis produced by many bacterial filtrates (B. typhosus, B. pyocyaneus) is to be explained by the presence of an alkali elaborated in the growth of the organism. The filtrates used in our tests have all been faintly acid to phenolphthalein.

The animals selected for the injection experiments were dogs and rabbits; the former receiving five to twenty cubic centimetres (dose 1:1514 to 1:235) of the filtrates in either the saphenous or mesenteric vein; the latter one to twenty cubic centimetres (dose 1:1790 to 1:64) in either the mesenteric or marginal ear vein. In all, twenty-nine injections have been made; in no instance did death occur as the immediate result of the injection. Necroses of the liver occurred in ten of the animals. Two of these we have thought best to exclude because of associated coccidiosis, although the necroses appeared to be entirely independent of the parasitic invasion; another has been excluded also because of the chronic character of the lesion. The remaining seven cases exhibited typical necroses; two occurring in dogs and five in rabbits. These lesions followed the injection of filtrates of the typhoid bacillus in three cases, of the hog-cholera bacillus in three cases, and of the dysentery bacillus in one case. Filtrates of the B. pyocyaneus, S. pyogenes aureus, and S. pyogenes did not cause necroses. These necroses are not always visible to the naked eye, but when seen macroscopically they appear as miliary points, or occasionally as round or oval areas or linear streaks of grayish color, and distinctly separated from the normal liver tissue. They are very few in number compared to those produced by the agglutinins of cytolytic immune sera, and are usually limited to the superficial portions of the liver. Portions of the liver in contact with other lobes or adjacent organs are more frequently involved than the free surfaces. Histologically, the liver cells exhibit a hyalin necrosis, the nuclei being entirely destroyed, or evident merely as faint rings; fragmented or pyknotic nuclei were seldom seen. In many of these areas the vessels are filled with red blood corpuscles more or less altered and fused, and suggestive of hyaline thrombi. This condition, however, is not constant, and is not so evident as in the necrotic lesions produced by cytolytic immune sera. On the other hand, larger vessels, especially the smaller branches of the portal vein, contain typical agglutinative red corpuscle thrombi more or less completely occluding the vessel. Similar thrombi of small vessels have been seen in other organs, as the kidney, spleen, and lymph nodes, but without definitely associated lesions. Other thrombi, as those composed of endothelial cells, fibrin, etc., have not been seen in the liver.

Fatty changes in the liver and kidney, intense congestion of the spleen and lymph nodes, and a proliferation of the endothelial cells of the lymph sinuses have been found not infrequently after the injection of typhoid and hog cholera filtrates. A relation between these lesions and the injected fluids cannot, however, be readily demonstrated; the proliferation of endothelial cells, especially, is not infrequent in apparently normal animals. That some serious injury to the kidney is brought about is indicated by the appearance of albumen in the urine after the injection of filtrates of B. typhosus and B. dysentriæ.

The results of the injection of filtrates of typhoid and hog cholera bacilli grown upon blood media, while very suggestive, are not conclusive, owing to the small number of observations. But six filtrates so grown were injected. Filtrates of the typhoid bacillus grown in blood suspensions, while possessing an increased agglutinating power *in vitro,* did not cause necroses upon injection; on the other hand, two different filtrates of the same culture grown for several days on sterile rabbits' organs caused the most extensive lesions observed in the course of this investigation. The bacillus of hog cholera grown in blood suspensions caused, in one instance, lesions in the liver. The attempt to produce necroses with such filtrates has therefore been successful in three of six experiments; while with filtrates of the same organism grown on plain agar necroses resulted in three of twelve attempts. These results are suggestive in connection with the increased agglutinating power observed *in vitro,* but the small number of experiments does not warrant definite conclusions.

Filtrates of B. typhosus grown in heated rabbit serum produced no lesions upon injection into rabbits.

CONCLUSIONS. The filtered autolyzed products of a number of bacteria possess hemagglutinins of low activity; the formation of these may be stimulated by previously growing the microorganisms on media containing fresh red blood cells. The injection of these filtrates into dogs and rabbits is followed in some instances by the occurrence of liver necroses with associated fused red blood corpuscle thrombi; like thrombi may occur in other organs. These thrombi are similar in structure to those generally described as hyaline thrombi. The demonstration of agglutination *in vitro* and the association of the fused red cells with the liver lesions suggest a relation of the agglutinin to the lesions. This relation, however, cannot be considered as proven, for it is impossible to exclude the effect of toxins acting directly upon the liver cells; on the other hand, the similarity of the lesion to the very definite necroses caused by he powerful agglutinins of cytolytic immune sera strongly supports the possibility of such a relation.

The results observed by us are in accord with the slight potency of the agglutinin obtained. It is probable that methods which cause a more complete disintegration of the bacterial cells, as those employed by Vaughan[25] and by MacFadyan and Rowland,[26] would yield an agglutinin as powerful, comparatively, as the toxins so derived, and capable of producing lesions more analogous to those caused by the agglutinins of cytolytic immune sera.

We present this communication, therefore, not as an attempt to prove that all hyaline thrombi are composed of fused red blood corpuscles, or that all liver necroses are caused by such thrombi, but rather to indicate the evidence in favor of the view that these lesions, in some instances, may be due to bacterial hemagglutinins.

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COMPLICATIONS AND DEGENERATIONS OF UTERINE FIBROMYOMATA.

A PATHOLOGICAL AND STATISTICAL STUDY OF TWO HUNDRED AND EIGHTY CASES.

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INTRODUCTION

Recent discussions in the surgical and gynecologic branches of the American, British and French medical organizations, indicate a renewed interest in the question of treatment of uterine fibromyomata. This is due largely to facts brought forth as the result of the systematic routine pathologic examination of all "fibroid" tumors. The frequency with which fibroid tumors present degenerations and are accompanied by complications has upset the classical teaching in regard to prognosis and treatment of these growths. More particularly has interest been stimulated in regard to the so-called "malignant degenerations," as is evidenced by the prominent place which carcinoma and sarcoma occupy in recent publications on myoma. At present, however, the results of pathologic studies are not definitely collected, and there is a lack of statistical comparison. The importance of bringing together such results is evident, for the question of operative interference and extent of operation must depend on information derived from combined clinical and pathologic reports. In regard especially to the extent of operation are the results of pathologic investigation of value. While in the removal of a benign tumor it is without doubt ideal that the patient should suffer as little mutilation as possible, still that operation must be done which offers the least danger, and at the same time takes into consideration the various attendant complications. On this point recent investigations indicate that the complications of myomata are by no means to be lightly considered.

Aside from the tumor itself, the adjacent organs must be taken into account. The question of the condition of the ovaries is important from the fact that in supravaginal hysteromyomectomy the trend of opinion among gynecologists is that an ovary should be left in order to ameliorate the severe menopausal symptoms sometimes produced by complete ablations. For this reason the microscopic study of these organs is important in order to determine the frequency of disease of the ovary in connection with myoma.

Also, after hysteromyomectomies and myomectomies, the possibility of infection from a diseased tube is of importance, not only as concerns the union of the wound, but also as regards the mortality of these operations. Hence the examination of the tubes for salpingitis, pyosalpinx, etc., is of no slight value.

In the study which is here presented, an attempt has been made to determine the frequency of the various degenerations and complications and to base thereon certain general conclusions concerning treatment.

GENERAL LITERATURE

Since Martin[1] in 1888 made his study of degenerations in 205 cases of fibromyomata, others have reported similar series, notably Noble,[2] 258 cases; Cullingworth,[3] 100 cases; Mary Scharlieb,[4] 100 cases, and Frederick,[5] 125 cases. Combined, these make 788 cases available for the classification as to degenerations. There is some slight difference in the classifications of the five writers, but by taking certain liberties with their tables,* the degeneration may be summarized as follows:

Fatty degenerations	7
Calcareous infiltration	11
Necrosis	55
Cystic degeneration	34
Telangiectasis	46
Sarcoma	17
Associated carcinoma cervicis	15
Associated carcinoma corporis	17
Myxomatous (edematous)	8
Associated syncytioma [6]	1

(Total number of cases, 788.)

Martin has not estimated his complications; so for the purpose of that classification only the series of Noble, Cullingworth, Mary Scharlieb and Frederick are available They are as follows:

Appendicitis	13
Hydrosalpinx	41
Hematosalpinx	2
Ovarian cyst	32
Dermoid cyst	5
Ectopic pregnancy	4
Papillary carcinoma of ovary	2
Pyosalpinx	18
Salpingitis	10
Abscess of ovary	7
Tubo-ovarian abscess	1
Dilated ureters and hydronephrosis	1
Dilated ureter, hydronephrosis and pyelitis	1
Parovarian cyst	3
Cystic ovaries	18
Hematoma of ovary	1

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*In this table associated tumors are arbitrarily included. Martin's ten cases of suppuration are placed under necrosis. Noble's case of syncytioma is retained, although there is some doubt from the pathologic report as to whether there was a fibroid associated with the new growth. This tumor was twice reported. The following extract is from the second publication, pathologic report by Dr. Babcock: "In the early description of the growth it was described as a sarcomatous or endotheliomatous degeneration of a fibroid tumor; but restudy gives no evidence that fibromuscular tissue is present more than would accompany the growth of the syncytial tumor. It is believed that this is a primary syncytioma malignum in a uterus not the seat of any other tumor."

Tubercular peritonitis	1
Universal adhesions	22

(Total number of cases, 583.)

In making this compilation a great difference in classification was apparent. Frederick and Mary Scharlieb alone mention cystic ovaries. Cullingworth in his 100 cases does not mention salpingitis. Many complications of a purely clinical nature, as retroversions of the uterus, etc., have been eliminated in order to bring the classification in accord with that of this paper.

In a more recent publication, Daniels[7] in 124 cases found pathologic lesions in the appendages or their immediate neighborhood in seventy-two; in seventy cases of complicated fibromyomata, lesions were confined to the ovary in twenty-eight, to the tubes in twelve, and involving both in thirty.

Marscher[8] in twenty-two cases of myomata found ectopic pregnancy in one and suppurative diseases of the appendages in four.

Bond[9] reports fifty cases, in which eight had tubal disease, which he claims was due mainly to infection from miscarriage.

Hunner[10] in a series of 100 consecutive cases occurring in Kelly's service found pyosalpinx or tubo-ovarian abscess in six cases, hydrosalpinx or perisalpingitis in fifteen cases and ovarian cysts in nine cases. There was found in association malignant disease in seven cases; sarcoma in two, adenocarcinoma of the fundus in three, and squamous carcinoma of cervix in two.

Other writers have reported smaller series of cases or series devoted to one complication as appendicitis[11] or salpingitis[12]. As these reports do not include all complications they have not been quoted.

From this summary it will be seen that the complications of fibromyomata are many and varied. It will be noted that tubal complications form a very large percentage in Daniel's series, while in the combined series they are not prominent; also in the latter series pyosalpinx is numerically greater than salpingitis. This may, I think, be explained by the fact that the earlier writers did not have a complete microscopic examination of the condition of the tubes. Frederick mentions cystic ovaries which occurred in about fourteen per cent. of his cases. Mary Scharlieb estimates ovarian cysts and cystic ovaries together as twenty-three per cent.

In regard to associated malignant tumors in the combined series, carcinoma occupies a relatively high place. No distinction is made between "sarcomatous degeneration" of a myoma and of sarcoma associated with myoma except in Martin's paper. Of the more recent publications on sarcomatous degeneration of fibroids, Baker and Graves[13] publish thirty-three cases of fibroid tumors, in which three were sarcomatous. The percentage is truly large; but this is similar to the findings of Ulesko-Stroganowa,[14] who reported before the Russian Society for Obstetrics and Gynecology, March 22, 1902, 100 cases of fibromata with ten cases of malignant degeneration. From the description these are evidently divided into two groups, leiomyoma malignum and true sarcoma. It is not quite clear what is meant by the former. In the discussion which followed, her views were generally opposed. From the abstract of her paper it is impossible to say how many of these were really sarcomatous.

Tate[15] and Bertha Van Hoosen[16] each report a case of sarcomatous degeneration of fibromyoma, which will be referred to later under the special heading.

From these papers it will be seen that "sarcomatous degeneration," while not common, is sufficiently so to merit further study; first, in regard to its frequency, and second, as to whether it is a true transformation of a myoma or merely an associated but independent growth.

MATERIAL

The material on which this study is based* represents seven years' service of a general hospital (Albany Hospital), and includes all myomata removed during that time. Complete gross and microscopic examinations have been made in all cases. The series also includes 26 cases in which myomata were found at autopsy.

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*I wish to express my thanks to the operators from whom these cases came, more particularly to, the surgeons of the Albany Hospital. I also wish to express my gratitude to Dr. Blumer, late director of the Bender Laboratory, and to his assistants, whose conscientious routine examinations and exhaustive records have made this report possible. I also wish to express my sincere thanks to Dr. R. M. Pearce, present director of the laboratory, for constant assistance and encouragement.

SUMMARY OF 280 CASES OF FIBROMYOMATA.

Character:—

Single	110
Multiple	170
Small	79
Medium	59
Large	99
Very large	43
Subserous	67
Interstitial	85
Submucous	23
Combined	105

Degenerations—

Slight hyaline	18
Moderate hyaline	32
Marked hyaline	19
Hyaline and calcareous	8
Calcareous	14
Calcareous, necrotic, hemorrhagic	2
Cystic	8
Myxomatous	4
Hemorrhagic	6
Necrotic	4
Necrotic and hyaline	3
Necrotic, cystic, infected	1
Adenomyoma	6
Associated with adenocarcinoma	6
Associated with squamous cell carcinoma of cervix	2
Sarcoma	3
Deciduoma malignum	1

Complications—

Ovarian cysts	15
Parovarian cysts	2
Cystic degeneration of ovaries	55
Tubo-ovarian cyst	1
Calcification of ovary	1
Ovarian fibroma	2

Ovarian carcinoma	2
Salpingitis	38
Salpingitis and hydrosalpinx	3
Salpingitis and tubo-ovarian abscesses	3
Pyosalpinx	5
Pyosalpinx and tubo-ovarian abscesses	2
Extra uterine pregnancy, salpingitis and hydrosalpinx	1
Hydrosalpinx	6
Hydrosalpinx and tubo-ovarian abscess	1
Autopsies—	
Total number	26
Deaths due to tumor	2

PATHOLOGY

Character.—All these variations in fibroid tumors are familiar to operators and pathologists. "Multiple" in this series is taken to mean more than one tumor. The division as to size has been based on the following scale: Small, up to four centimetres; medium, four to eight centimetres; large, eight to sixteen centimetres; very large, above sixteen centimetres in diameter. In multiple tumors the diameter of the largest tumor was taken as the determining factor. The largest tumor noted weighed ninety pounds, and measured roughly 50x40x20 centimetres. The tumor was single, showed considerable necrosis and calcareous degeneration, and caused pressure symptoms which brought on the death of the patient. It was removed postmortem. Several other tumors were noted between forty and fifty pounds. It will be noted that 142 tumors measured more than eight centimetres in diameter.

The analysis as regards position was not easy, as it is not always plain into which of the classes a tumor should go. I regret that there is excluded a most important class of broad ligament fibromyomata, of which the data at hand would not allow a proper estimation.

By "combined" is meant multiple tumors, one each of which may be classed in one of the divisions. Thus it is seen that there are sixty-five multiple tumors which fall into one class (always interstitial or subserous), and 105 multiple which fall into at least two classes.

In one case of multiple fibromyomata a medium-sized fibroid had become detached from its pedicle and lay retroperitoneally, being nourished by the mesenteric vessels. Similar cases have been reported by Alban Doran[17] and others.[18]

The comparative infrequency of submucous myomata is noticeable.

Simple Degenerations.—In tumors of such size (142 above 8 centimetres diameter) it is remarkable that a large number with degeneration, particularly with hyaline degeneration, was not met with. The combination of hyaline and calcareous degeneration in eight cases is of interest. It would seem that the tendency of these tumors is to undergo progressive hyaline change going on to calcareous degeneration.

The twenty-three examples of calcareous degeneration existed in old women, but one being below fifty. These varied in consistence from those of the "Wombstone" type, ten centimetres across, to those with discrete, moderate calcareous deposits.

In the consideration of cystic degeneration, as Alban Doran[19] shows, a distinction should be made between true cystic degeneration and necrosis going on to cavity formation. In this series, however, his standard of judgment that a "fibroid is not truly cystic unless it includes a cavity containing half a pint of fluid," has not been adhered to, but tumors with smaller cavities have been judged as truly cystic. There were no cysts of large size found, the largest containing approximately 1,000 cubic centimetres of fluid. Cystic degeneration is more especially interesting from the fact that of Graves' four cases of cystic degeneration three were sarcomatous, evidently a necrosis going on to cyst formation. Mary Scharlieb's series shows six cases of sarcomatous degeneration, and of these three were cystic.

Necrosis and Inflammation.—All stages of inflammation and necrosis were noted. Necrosis occurred mainly in large subserous tumors, and was evidenced, on section, by brownish-yellow areas. There was usually considerable associated odema. In four cases this went on to liquefaction of the central area. It is interesting to note in regard to the possibility of infection that two cases were associated with salpingitis and two with hydrosalpinx. One large submucous tumor with multiple interstitial nodules was necrotic and sloughing. In all cases of sarcomatous degeneration, hemorrhage and necrosis were noted.

Adenomyoma.—The percentage of these tumors is about that usually found. They offered in this series nothing of special remark in the gross appearance. One showed marked hyaline change and one calcareous degeneration.

Malignant Changes.—Sarcomatous degeneration was found in three cases. There was no definite appearance by which these sarcomatous changes could be recognized. The main characteristics were necrosis, with broken-down areas and discolored spots from recent and old hemorrhages. A yellowish-white glistening growth could be distinguished in one case infiltrating the muscle and surrounding the necrotic areas. During the period from which these reports were taken six cases of sarcoma of the uterus occurred, in addition to these three cases of sarcomatous degeneration of uterine fibroids.

In case one it was possible to make a diagnosis in the gross specimen, as the disease had infiltrated the uterine tissue and gave a semi-necrotic appearance with irregular, hemorrhagic, pinkish areas devoid of fibrous arrangement, and a shell of malignant tissue infiltrating the tumor.

Cases two and three were also necrotic, soft and friable, and in the macroscopic examination were taken for necrotic fibroids.

Chorio-epithelioma infiltrated one case of fibroid tumor.

This is, so far as is known, the first authentic instance of such invasion reported. Complete reports of these four specimens from the records of the Bender Laboratory follow:

CASE I.—Mrs. M. N. Specimen consists of uterus with tubes and ovaries. One tube and ovary are separate from the rest of the specimen, the tube having been amputated at the junction with the uterus.

Uterus.—The uterus is greatly enlarged and measures 19 cm. long and about 14 cm. in diameter. Except for an irregular area about 7 cm. in diameter corresponding to the fundus, the peritoneal surface is everywhere covered with firm adhesions. Near the superior surface of the fundus are two globular tumor masses the size of a cherry, which are attached to the body of the uterus by a slender pedicle of peritoneum and fibrous connective tissue. Near the above tumor can be seen a pea-sized submucous tumor similar to the above. On section these tumors are pearly white with fine whorls of connective tissue. Adjacent to the origin of the attached tube projects a tumor mass about 3½ cm. in diameter which is soft and on section shows a thin capsule with central contents similar to that of the cavity of the uterus. On section the cavity of the uterus is found to be filled with a necrotic mass, the core of which is the size of an orange, and of a pinkish, yellow color with the consistency of liver tissue. This central mass shows whorl-like markings suggesting the cross-section of a large fibromyoma. Extending from the central core and infiltrating into the muscular coat is a stratum of extremely friable tissue from 2 to 4 cm. in thickness. This stratum is throughout semi-necrotic and shows irregular hemorrhagic areas, while at the outer border is an irregular zone which on section presents a jelly-like whitish glistening surface. The muscular coat of the uterus is under considerable tension, retracting rapidly when cut. This muscular coat has an average thickness of about 5 mm., but in many places is not over 2 mm. in thickness. The boundary between the muscular and semi-necrotic mass is nowhere sharply drawn, so that the muscular coat appears to be infiltrated by the mass lying beneath it. Near the fundus of the uterus, the muscular wall is much thicker than elsewhere. On section there is disclosed a definitely encapsulated tumor mass the size of a hen's egg which readily separates from the capsule and presents on section a soft, dark red, irregularly mottled surface. It is connected by a broad isthmus to the mass occupying the cavity of the uterus.

Tubes.—The attached tube is markedly congested, but otherwise apparently normal. Opposite tube is the same.

Ovaries.—The attached ovary is cystic throughout, having numerous cysts ranging from the size of a pigeon's egg to that of a pea, the substance of the ovary being crowded to one side. Opposite ovary shows very many cysts ranging from 2 to 10 cm. in diameter. These cysts contain clear straw-colored fluid.

Anatomic Diagnosis.—Sarcoma of uterus with necrosis and hemorrhage.

Microscopic Description.—Tissues, uterine wall, ovary, polypoid tumor described in gross description. Uterine wall: Sections taken through portion described as capsule in gross description show smooth muscle infiltrated with masses of spindle-shaped cells having large clear staining vesicular nuclei and little protoplasm. Among these cells are seen large irregular cells, the nuclei of which have a lobulated outline. Indistinct mitotic figures are seen in some of the cells. These cells have an utterly lawless arrangement, and deeper in the sections they form a continuous mass containing numerous thin walled blood vessels. Many of the sections show hemorrhagic areas with red blood corpuscles in various stages of degeneration. Some sections show simply masses of necrotic cells.

Polypoid Tumor.—Body of tumor shows smooth muscle largely replaced by fibrous tissue, while the pedicle of the tumor is seen to be infiltrated with cells similar to those described in tumor of the uterine wall.

Ovary.—Shows large follicular cysts and corpora lutea undergoing organization.

Microscopic Diagnosis.—Uterus with fibromyomata invaded by spindle-celled sarcoma; necrosis; hemorrhage; follicular cysts of ovary.

CASE 2.—Miss S. A. T. Specimen consists of an irregular mass of tissue composed of uterus and appendages and measures 18 x 13 x 7 cm. At one portion is attached a normal Fallopian tube, which measures 11 cm. in length, and an ovary 1 x 2 x 2½ cm. which has undergone fibrous change. On section the irregular surface of the mass is found to be due to the presence of large, roughly spherical tumors, varying in size from 2 to 11 cm. in diameter. The original form of the uterus can not be made out. The cavity of the uterus is pale and covered with a somewhat sticky secretion. The tumor masses which lie in the myometrium, on section, have the characteristic appearance of myomata; one of the large tumor masses has undergone degeneration, is soft and friable, and contains a considerable amount of blood. Immediately beneath the serous coat are a number of small pedunculated tumor masses which average 1 cm. in diameter. On section these are similar to the large tumor masses.

Anatomic Diagnosis.—Multiple interstitial and subserous myofibromata of the uterus. Normal Fallopian tube. Fibroid ovary.

Microscopic Description.—In places a definite picture of fibromyoma may be seen. Adjacent to such areas and differentiated from it only by the difference of structure are areas of typical spindle-celled sarcoma. The sarcomatous tissue is extensively necrotic, the necrosis in places being universal, and in other places sparing the cells immediately about the vascular channels. The necrotic areas are infiltrated with leucocytes. Necrosis is seen as well in the myomatous portion, but is not so prominent.

Microscopic Diagnosis.—Fibromyoma invaded by spindle-celled sarcoma.

Case 3.—Mrs. S. E. Specimen consists of about twenty-five separate pieces, which in aggregate make a mass about the size of a man's hand. One large globular mass measuring about 18 cm. in diameter makes up the bulk of the specimen. This mass presents a convex smooth surface covering about three-fifths of the mass. This surface is smooth, pale pink in color, part of surface being glistening and part of it showing firm, blood-stained connective tissue bands. The remaining periphery of this mass is exceedingly irregular and consists of various sized strips of tissue which are soft, friable and deeply stained and show numerous large blood vessels. The contents of many of the blood vessels consist of a firm coagulum. These shaggy strips are distinctly necrotic and are undoubtedly further represented by the numerous small pieces of semi-necrotic material which go to make up the remainder of the specimen. The comparatively smooth surface of this mass is irregularly lobulated and shows beneath the surface a number of small cysts filled with clear amber-colored fluid, also numerous pea-sized to cherry-sized spherical tumor masses, some of which present on cross-section a pearly white glistening surface with a whorl-like arrangement of the tissue elements. On section of the large tumor mass, the cut surface presents a thin cortex varying from 2 to 10 cm. in thickness composed of a firm, pinkish-white tissue beneath which is a whitish, coarsely granular surface showing the remains of numerous small cysts, most of which are filled with a blood-stained fluid. As one gets further away from smooth surface the secton becomes considerably blood stained and takes on a yellowish necrotic look and the cysts become larger in size until finally the semi-necrotic shredded mass described above is reached. The small pieces accompanying this specimen consists of stringy masses of distinctly necrotic tissue similar in character to that described as occurring in the center of the large tumor mass. One of the larger pieces accompanying the specimen is thin, averaging about 1 cm. in thickness, and has on its smooth side considerable adipose tissue and resembles in consistency, on cross-section, the firm tissue described as forming the capsule in the main tumor mass. No evidence of tubes and ovaries.

Anatomic Diagnosis.—Degenerated myoma of uterus.

Microscopic Description.—Sections through portion described as capsule of large tumor show thin layer of smooth muscle tissue with invading masses of medium-sized cells having rather darkly staining oval or spindle-shaped nuclei and little protoplasm. Many irregular mitotic figures are seen among these cells. The deeper, softer portions of the tumor are seen to be composed of solid masses of these cells. Numerous thin-walled blood vessels are seen in the cell masses. No evidences of necrosis are seen. Many blood vessels at the periphery of the tumor are completely plugged with the tumor cells. Sections through nodular masses at surface of tumor show smooth muscle tissue rich in cells and a moderate amount of fibrous tissue.

Microscopic Diagnosis.—Myoma of uterus invaded by spindle-celled sarcoma.

Case 4.—Mrs. C. R. Specimen consists of an enlarged uterus measuring 11 x 6 x 5 cm. Peritoneal surface is smooth. The walls are for the most part normal. At one point there is a typical myoma one centimeter in diameter, with a hemorrhagic center. Springing from the mucous membrane are a number of cauliflower-like excrescences over areas varying from 1 to 2 cm. in diameter. These project .5 cm. above the surface of the mucoso, some of them ulcerated, covered by little papillary projections and distinctly hemorrhagic. On section they appear to be part of the new growth which extends down into the uterine musculature. This growth is for the most part distinctly hemorrhagic, though in one or two places of a homogenous white color. In the uterine musculature of the fundus is a small cavity, about a centimeter in diameter, into which projects a number of pinhead-sized, congested, papillary excrescences.

Anatomic Diagnosis.—Adenocarcinoma of the uterus (?). Small interstitial myoma.

Microscopic Description.—Section presents a small piece of typical fibromyoma, at one side of which is a large hemorrhagic mass. The line of separation from blood clot is not distinct. The adjacent portion of tumor shows some lymphocytic infiltration. This hemorrhagic mass shows throughout some necrotic tissue with irregular strands and masses of syncytial tissue composed of cells with a large amount of protoplasm and large deeply staining nuclei. The outlines of these cells are not always distinct owing to the fusing of their protoplasm. The syncytial cells are found everywhere in the midst of hemorrhage. The necrotic tissue is moderately infiltrated with leucocytes. The nuclei of the large cells are often irregularly stained, sometimes are so arranged as to give the appearance of giant cells. These masses are in direct continuity with the myoma; in several places a distinct invasion is evident.

Microscopic Diagnosis.—Fibromyoma of the uterus infiltrated with chorio-epitheloma.

Relation to Cancer.—Adenocarcinoma of the fundus was associated with fibroid tumor in six cases; in two of which the fibroid was infiltrated by the carcinomatous tissue.

In five of these cases the uterus was the host of interstitial fibroids of small or medium size. When the relative frequency of adenocarcinoma and squamous cell carcinoma is considered it will be seen that we have here a much higher percentage of adenocarcinoma than is found in the usual run of cancer cases complicated and uncomplicated by fibroids. This agrees with Martin's estimation.

Squamous cell carcinoma of the cervix occurred in two cases. In both cases the fibromata were interstitial and very small.

In view of the relative frequency of adenocarcinoma and fibromata of the uterus, it would seem that the association of the two are worthy of consideration. If the percentage of fibroids at autopsies, 14.8 per cent. (*v. infra*), be taken as an approximate ratio of their occurrence, it seems at least that while the association of squamous carcinoma with fibroids is accidental, the occurrence of adenocarcinoma may be more or less influenced by the presence of fibroid tumors. In this connection statistics compiled from the records of institutions having large series of cases and autopsy reports would be of value.

Complications. — Ovarian cysts occurred in thirteen cases and varied in size from six to twelve cm. in diameter;

but one was of the papillomatous type. Seven of these cases were additionally complicated by salpingitis.

The two parovarian cysts were of moderate size, about six to eight centimetres in diameter. One tubo-ovarian cyst existed, and was of moderate size.

The ovarian fibromata measured 8x7x4.5 and 20x11x10 centimetres, respectively. The latter was associated with a very small interstitial fibroma of the uterus. Of the two cases of carcinoma of the ovary, one was bilateral, and in both instances the growths were due to metastases from a tumor of the breast.

Cystic ovaries (one or both) in fifty-five cases (twenty per cent.) may seem to be a large percentage, but compares very closely with Scharlieb's[4] estimation of this complication. These are due, it is thought, to the undue thickness or toughness of the ovarian boundaries. There is in almost all these ovaries an increase in the amount of fibrous tissue.

Tubal Complications..—The tubes were diseased in sixty cases; of these thirty-eight were salpingitis alone. In several cases the gross change was slight and the diagnosis made microscopically. In twelve cases there was pus in the appendages in the form of pyosalpinx or tubo-ovarian abscess. There were also eleven cases of hydrosalpinx, of which five were additionally complicated by salpingitis, tubo-ovarian abscess or ectopic pregnancy. One case combines all three—ectopic pregnancy, salpingitis and hydrosalpinx.

It will thus be seen that the ovaries, tubes and adjacent neighborhood were diseased in a large number of cases. Alban Doran states that his experience is more like that of Cullingworth, who found no disease in the appendages save five cases of hydrosalpinx in 100 fibroids. Lawson Tate and Twambly,[20] on the other hand, imply that this condition exists in fifty per cent. of all cases of fibroids. Daniels found disease of the appendages in fifty-eight per cent. of his cases. In this series (including fifty-five cases of cystic ovaries) the appendages showed disease in 137 cases, or forty-nine per cent. In addition to these cases there were many cases in which the remains of adhesions were noted, but as it was obviously impossible to estimate this with exactness, without description of the appearance *in situ* at the time of operation this complication has not been noted.

Myomata in Routine Autopsy Work.—On examination the records (Bender Laboratory) of autopsies on women show that fibromyoma of the uterus was found in twenty-six. In two cases apparently death was indirectly caused by the tumor. To what extent the inter-current disease, which was the cause of death in other cases, was hastened in its course by the associated fibroids, can not be deducted. The tumors were large in three (greater than eight centimetres diameter); small in twenty cases (less than four centimetres diameter), of these last ten were single and ten multiple. The age at which these patients died in decennial periods were as follows: Under thirty-five, three; between thirty-five and forty-five, six; between forty-five and fifty-five, six; between fifty-five and sixty-five, six; between sixty-five and seventy-five, four; above seventy-five, one. The youngest was twenty-eight; the eldest seventy-eight. The influence of the tumor was apparent in one case in which death was due to anemia and nephritis; a large submucous tumor by pressure had caused hydroureter and uterine hemorrhages. In a second case a large fibroid tumor of ninety pounds by pressure had caused hydroureter and venous congestion with edema of the lungs. In this case the weight of the woman, less the tumor, was sixty-five pounds. The other cases, which were probably influenced by the fibroid tumor, are deaths from pyonephrosis, pyelitis, rupture of bladder and acute peritonitis. Bishop[21] has collected thirty-seven fatal cases of fibromyomata.

Of the twenty small tumors, one was complicated by tubo-ovarian cyst and hydrosalpinx. Four were associated with adhesions, and one with carcinoma of the ovary secondary to mammary cancer.

Of the medium sized tumors, of which there were three one was associated with bilateral pyosalpinx which had caused a general peritonitis. The tumors in this case were three in number and interstitial.

The total number of autopsies done on women over twenty years of age, during the seven years in which these autopsy reports were collected, amounted to 175. So that of all adult women coming to autopsy, 14.8 per cent, or one in every seven, had uterine fibroids. From this it may be seen that small fibroids of the uterus may cause little or no disturbance, and that many of these tumors cause no symptoms and are not discoverable during life. The danger of these growths, apart from submucous tumors, is due to their complications, and while these may not always endanger life, it is evident that they frequently cause sufficient disturbance to produce alterations in the surrounding tissues, as is shown by the presence of adhesions, etc.

RELATION OF PATHOLOGIC CHANGES TO TREATMENT.

In conclusion, what deductions can be drawn from this series? So much has been written by men of wider experience that it would be a work of supererogation to add to their well-debated advice. But there are a few questions to be considered:

First, in regard to the advice we must give to a patient suffering from fibroid. It is well understood that the operation for fibroids, in the hands of capable operators, is in uncomplicated cases practically devoid of danger. It is to complications and degenerations that mortality in fibroid tumors is due, as we know from experience and from published reports. Delay in an uncomplicated fibroid exposes the patient to the possibility of the development of complications. And with the large percentage of complications in this series it is evident that with delay the liability to complication is increased. While this is so, it is evident that there is one class of fibroids which may cause few or no symptoms, viz., the small subserous and interstitial tumors. We may, therefore, say that delay is justifiable only in these latter cases and not justifiable in even these when complications exist.

In reference to the extent of operation, while it is obvious that myomectomy is the ideal operation, there is no doubt that it is only applicable to a small class of cases—those in which the tumors are easily accessible and in which it is possible to eradicate them completely. If eradication is not complete, there is the possibility of renewed growth, and should pregnancy occur, with its increased blood supply, this possibility is the greater. This should be kept in mind, as those cases in which myomectomy is desirable are usually childless women.

It is at present accepted that the operation of supravaginal hysteromyomectomy[22] is accompanied by the lowest mortality[23]. But this operation is obviously not applicable to those cases with malignant degeneration and associated with malignant disease of the uterus. Such cases demand complete extirpation of the cervix. Should, however, the commonly accepted operation of supravaginal hysteromyomectomy be attempted, and on opening the uterus adenocarcinoma or suspicious necrotic change be seen, the cervix may be removed and a complete ablation done.[24]

Adenocarcinoma and sarcoma are the forms of malignancy which, in connection with fibroids, are most likely to come to operation unrecognized. If, however, the case be uncomplicated by malignancy, the choice must lie between amputation through the cervix and myomectomy. It is rarely advisable to do myomectomy when the appendages are adherent or in the presence of old or recent infection. The site of enucleation may become the starting point of a peritonitis.[25] In view of the large percentage (21.4) of diseased tubes, it is evident that myomectomy is limited to a small class of cases.

Should amputation through the cervix be the operation of choice, one or both ovaries may be left to ameliorate the symptoms of the surgical menopause. In such cases not only must the question of infection from the tubes be considered, but also the condition of the ovary. In a large percentage of this series cystic ovaries were found. A cystic ovary should not be left; if necessary, resection may be done and the cysts removed.

CONCLUSIONS

First. Fibroids which are producing symptoms, and all fibroids except those designated as small (especially when subserous or intramural), should be removed, because the risk to the patient from operation is far less than that from the tumors themselves.

Second. In view of the sarcomatous changes, carcinomatous associations and complications of uterine fibromyomata, early removal is indicated when they are of sufficient size to produce symptoms. Small uncomplicated tumors not producing symptoms do not require early treatment.

Third. Thorough pathologic examination should be made of all fibroids for evidence of malignancy. Particular study should be devoted to those tumors which are necrotic, cystic or both, as among these are found the largest proportion of malignant changes.

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A PECULIAR HYPERTROPHY OF THE PROSTATE, ACCOMPANIED BY AN ASCENDING INFECTION AND CYSTS IN THE URETERS, WITH A GENERAL DISCUSSION OF URETERITIS CYSTICA.

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While hypertrophy of the prostate is of common occurrence, the peculiar form to be described is unusual and explains some of the difficulties of catheterization and cystoscopic examination met with in this condition. The formation of cysts in the mucous membrane of the ureter is, on the other hand, much less frequent, being noted but twice in the records of over 600 post-mortem examinations at the Bender Laboratory. Previous to 1894 Lubarsch[1] cites but ten cases in the literature and found the condition himself in four out of 3,000 sections.

Following is a brief summary of the two cases we wish to report:

CASE I.—(Bender Laboratory Records, autopsy No. 0-604). *Clinical History:* E. S., male, age 80, admitted to the Albany County Hospital, February 18, 1903. Patient complains of diarrhœa and difficulty in voiding his urine. Family history—negative. Past history—Has used alcohol freely. Denies any venereal infection. Present condition—The patient's mental condition is defective and he gives untrustworthy replies to questions relating to his illness. He has used a metal catheter for some time, passing it himself without antiseptic precautions.

Physical Examination—The heart, lungs and abdomen negative. The rectum is prolapsed. The left testicle is apparently swollen, tense and transmits light and is about 8 centimetres in diameter. The prostate per rectum is found to be enlarged. There is a purulent discharge from the urethra. When the urine is withdrawn by a rubber catheter the first portion is pure pus and is followed by ammoniacal cloudy urine. Death ten days after admission, February 28, 1904.

Autopsy seventy-two hours after death by Dr. A. T. Laird.

Anatomical diagnosis.—Hypertrophy (fibro-myoma) of the prostate. Diphtheritic cystitis. Ascending infection (pyelo-nephritis) of both kidneys. Bilateral ureteritis cystica. Acute vesiculitis. Chronic interstitial nephritis. Chronic interstitial orchitis. Tuberculosis of epididymis and prostate.

Prostate—Shows hypertrophy, particularly in the lateral lobes, which cause obstruction to the outflow of urine, not, however, by pressure upwards as is seen with hypertrophy of the middle lobe, but rather by pressure downward. The chief hypertrophy is in the right lateral lobe, which extends across the upper wall of the urethra. It is peculiar in being attached to the lower portion of the gland by a thin pedicle which allows considerable mobility of the tumor. Extending outward in a lateral direction from the prostatic portion of the urethra is a pocket which measures 3 x 2 centimetres and which communicates with the bladder by a narrow orifice. Into this pocket the pedunculated lateral lobe fits, completely closing the communication between the bladder and the pocket, thus preventing the passage of urine and acting as a "drop latch." When a catheter is introduced it passes into the pocket and drains the pus which has accumulated there, at the same time it lifts the pedunculated lateral lobe allowing the urine to escape. The mucosa lining the pocket has a greenish grey color and is studded with fine miliary abscesses. The left lobe of the prostate is firm in consistency; the right lobe is softer than normal and nodular and on section the stroma predominates; small yellowish areas of glandular tissue are present. In the left lobe no glandular tissue can be found.

The Bladder is externally roughened and congested and attached to the adjacent coils of the small intestines by fresh adhesions. There are also extensive adhesions between the rectum and bladder. The bladder is dilated, its walls average 0.5 centimetre in thickness and it is infiltrated with pus throughout all its coats. The mucosa is covered with a seropurulent exudate and is of greenish color with here and there streaks of red.

The Right Kidney—Measures 9 x 5 x 3 centimetres. The capsule strips readily leaving a smooth surface. Beneath this are found a number of minute yellowish areas about 0.5 centimetre in diameter, which when sectioned appear to be made up of purulent material. The substance of the kidney appears normal, although the markings are somewhat indistinct. The pelvis of the kidney is dilated and the mucosa is congested.

Right Ureter—The mucosa is congested and about fifty small cysts project from it into the lumen. They have a glistening yellowish color and are filled with serous fluid which is under considerable pressure, spurting out when the cysts are punctured. In some cysts the contents are slightly tinged with blood.

The Left Kidney—Measures 7 x 4 x 3 centimetres. It has been converted into an abscess cavity and but very little of the normal kidney substance remains. The abscess cavity is lined by a purulent membrane. The mucosa of the pelvis is swollen and is covered with a purulent exudate.

Left Ureter—Is much dilated, measuring 1.5 centimetres in diameter. About a half centimeter from the ureteral orifice in the bladder several cysts are found, smaller, however, than in the ureter of the opposite side.

Seminal vesicles—Contain pus and yellow mucoid material.

Right testicle—Shows extensive atrophy. There is also a hydrocele measuring 10 x 4 centimetres.

Left testicle—The globus major of the epididymis is caseous and the interstitial tissue of the testicle is increased.

Urethra—Stricture of large calibre in the bulbous portion.

Histological Description—The cysts of the ureter are surrounded by a distinct membrana propria derived from the submucosa and are lined by transitional epithelium. The cyst cavities are filled with exudate often hemorrhagic, and containing desquamated epithelial cells. Among these are oval, pale, faintly staining bodies frequently showing nuclear shadows. The epithelium of the ureter is absent for the most part over the cysts; only a few strands of connective tissue separating the cysts from the lumen. Several of v. Brunn's cell nests are present in the submucosa; no lumen connecting them with the ureter can be found.

Microscopic examination of the cyst contents showed many epithelial and pus cells and bacteria. Peculiar round or oval highly refractive bodies containing vacuoles are also present and with Sudan III give the characteristic reaction for fat. Cultures made from the cysts showed the presence of the B. coli communis.

CASE II—(Bender Laboratory Records, Autopsy No. 0-323). L. G. R., female, aged 54. Autopsy, October 20, 1900, by Dr. G. Blumer.

Anatomical Diagnosis—Left renal calculus. Right ureteral calculus. Pyelitis on right side with atrophy of kidney. Cystic ureteritis. Pyelonephrosis with multiple miliary abscesses of kidney substance. Cystitis. Brown atrophy of heart muscle. Emphysema of lungs with hypostatic congestion and œdema. Cloudy swelling of the liver. Acute splenic tumor.

Left Kidney is greatly dilated and on section the pelvis is found to be enormously distended with thick greenish pus and contains a single yellowish white stone, granular in appearance (phosphatic). From it at one point a brownish stone projects, probably uratic (?) in origin. The removal of the capsule tears away the kidney substance which moreover is greatly diminished in amount. The surface of the kidney is congested and dotted with miliary abscesses.

Left ureter is markedly dilated and the mucosa is covered with little polypoid excrescences, perfectly round and translucent and average 1 centimeter in diameter.

Right kidney is greatly contracted and on removal of the capsule the surface is finely granular. On section the cortex is considerably diminished in amount. The pelvis of the kidney is dilated and contains thick pus.

Right ureter is blocked about 2 to 3 centimetres above its vesical orifice by several small stones.

Bladder contains thick muco-pus greenish in color. It is markedly contracted and the mucosa is congested.

Bacterioscopic—In the kidney abscesses was found a bacillus of the mucosus capsulatus group.

Histological Examination of cysts in the ureters. The cysts are located in the submucosa but project prominently into the lumen of the ureter, fully five-sixths of the cysts are above the level of the mucosa. The epithelium of the ureter has desquamated over the cysts leaving only a few strands of connective tissue. This connective tissue, derived from the submucosa, surrounds the cysts and also separates them from the lumen of the ureter. The lining of the cysts is composed of epithelium similar to that lining the ureter, that is transitional epithelium. At the base of the cyst are several layers of epithelial cells, but at the periphery where the pressure is greatest there are fewer layers and the cells are quite flattened. The contents of the cysts are in some cases colloid material similar to that found in the thyroid; in others, cellular debris. In the contents oval and refractive bodies, three to ten times the size of a leucocyte, are constantly present and in some of these faint bodies can be seen (nuclei). These are probably identical with the so-called sporozoa that have been described in association with cysts of the ureter.

Several of v. Brunn's cell nests are present in the submucosa. In one instance a connection between a nest and the lumen of the ureter exists.

FORMATION OF URETERAL CYSTS

Cysts of the ureter, pelvis of the kidney and bladder were first described by Rayer[2] and later by Rokitansky[3] and Morgagni[4]. Virchow[5] thought their formation in the ureter was due to a blocking of the crypts in the mucosa of the ureter followed by a retention of secretion; and in the bladder, on account of the presence of concentric bodies in the

To Illustrate Dr. Carey's and Dr. Laird's Article on "A Peculiar Hypertrophy of the Prostate."

Albany Medical Annals, July, 1904.

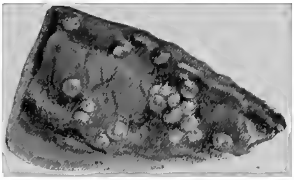

Fig. I —Shows the cysts in the mucosa of the ureter (actual size).

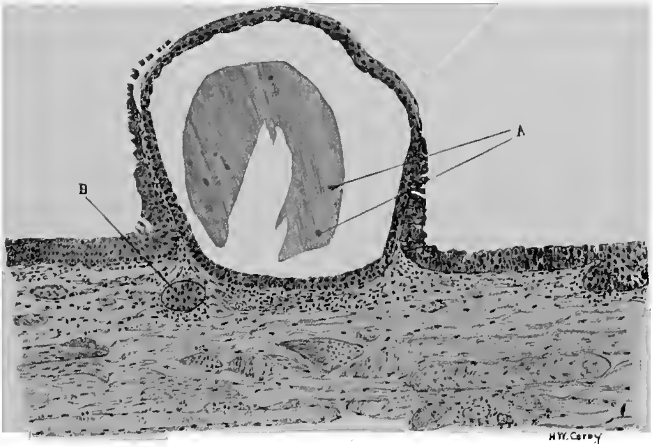

Fig. II.—Shows the structure of one of the cysts; the membrana propria extending entirely around the cyst wall. (A) are the bodies described as degenerated epithelial cells (so-called sporozoa); (B) a cell nest (v. Brunn); (objective, 1-6; ocular, I.).

cyst contents, attributed them to misplaced prostatic glands. Hamburger[6] described glands in the mucosa of the ureter which simulated the appearance of sebaceous glands and he thought the cysts originated from these. In a histological study of the ureter v. Brunn found nests of epithelial cells surrounded by a membrana propria and called attention for the first time to the peculiar arrangement of the connective tissue beneath the epithelium of the ureter. This arrangement is that of a meshwork with thickening at the nodal points forming septa which extend upward into the epithelial layers. The height of the septa varies inversely with the intra-ureteral pressure, being higher when the pressure is low. To variations in pressure v. Brunn[7] attributed the formation of these cell nests, small portions of the epithelium being enclosed and surrounded by the septa of connective tissue.

To determine whether cell nests were normally present Aschoff[8] studied the pelvis of the kidney, the ureters and the bladder in the new born and adult, but in no instance were they present, hence they are not constant elements. He discredits the influence of pressure in the formation of the cell nests.

Later investigations of Lubarsch[9], Marckwald[10], Stoerk[11], Zuckerhandl[12] and Paschkis[13] support the theory that the cysts originate from the cell nests of v. Brunn.

The method of formation of the cysts is described by Aschoff as follows:

(a) Enclosure of a portion of epithelium by septa of connective tissue with the formation of a cell nest. This causes small macroscopic nodules or granules in the mucosa of the ureter.

(b) Central degeneration of these cells accompanied by a transudation of fluid into cysts cavity.

The Location of Cysts is fairly constant and corresponds to the points of constriction in the ureter. They are almost constantly found in the pelvis of the kidney, upper third of the ureter and at the uretero-vesical orifice on the trigonum. They are frequently bilateral. In the two cases above reported the distribution of the cysts was diffuse and not limited to any portion of the ureter.

Etiology.—The exact cause of the formation of these cysts in the ureter is not known, but in the large majority of the cases reported they developed in association with inflammatory and suppurative conditions of the bladder, ureter and pelvis of the kidney (ascending infections).

In the twenty-four cases, including our two, a cystitis, calculus or pyelitis existed in all but two; in the latter no lesion of the urinary tract could be found.

Mention has been made above of the oval translucent bodies found in the cysts contents. These have been described as sporozoa by v. Kahlden[14], Pisenti[15], Silcock[16], Eve[17], Clark[18] and Sutton[19], and were believed to be the cause of the cyst formation. This view has not been supported by later investigations since the parasites could not be cultivated from the cysts and moreover it is improbable that any infection of this nature should always be limited to such a prescribed portion of the urinary tract.

The so-called sporozoa in our sections, while resembling parasites in some respects, were by no means constantly present in the cysts and never very numerous. They were never found outside of the cysts, in the lumen of the ureter or in the epithelium; where they were surrounded by cellular debris a gradual transition from epithelial cells to these so-called parasites could be traced. In some, several faint nuclei could be seen. It is our opinion that these parasitic like structures are an early stage in the degeneration of the epithelial cells lining the cysts and later become colloid. The interest in this condition of Ureteritis Cystica does not, however, relate entirely to its pathology. Aschoff has called attention to the fact that in the early stages of the formation of the cysts they may be mistaken for miliary tubercles in cystoscopic examinations.

In one of the cases reported by Marckwald the development of the cysts had been so extensive as to block the ureter completely, giving rise to great hydronephrosis. Healton and Gamgee[20] have reported a case in which haematuria had existed for many years and at autopsy a cystic villous papilloma of the renal pelvis was found. The bleeding, in part, was due to the rupture of the cysts.

Resumé

1. Hypertrophic lateral lobes of the prostate may be pedunculated and by their downward pressure on the urethra obstruct the outflow of urine, acting like a "drop latch."

2. The origin of cysts in the ureter is attributed to the central degeneration and later transudation of fluid into v. Brunn's cell nests.

3. Ascending infection of the urinary tract is the important factor in the etiology of these cysts.

4. The peculiar translucent oval bodies resembling sporozoa are in some instances the product of epithelial degeneration.

5. The cysts may, in their early stages, simulate miliary tubercles.

6. Cysts of the ureter may cause obstruction to the passage of urine from the kidney to the bladder with consequent hydronephrosis.

7. Rupture of the cysts can give rise to haematuria.

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INFANTILE INGUINAL HERNIA OF THE VERMIFORM APPENDIX WITH ADHESION TO THE EPIDIDYMIS.*

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Hernia of the appendix is not rare, but it is uncommon. Morgagni, in 1750, was, perhaps, the first to make reference to it. Scarpa reported several cases in 1806, after which we have series of cases reported by Klein, Brieger, Bajardi, Rivet, Gibbon, and others, until, in 1899, Peterson was able to collect 116 published cases, while Piersol, in 1901, estimated the number of reported cases as 125. That it is more frequent than the number of reported cases would lead one to believe appears from the fact that Coley found hernia of the appendix, without the presence of other portions of the intestinal tract, five times in 351 operations for femoral or inguinal hernia.

Hutchinson classifies hernia of the appendix into two divisions, congenital and acquired. The congenital form is always inguinal, and almost invariably occurs in the male sex and on the right side. In this form it is the rule to find adhesions between the appendix and some of the remains of the processus vaginalis—either to the wall of the sac, the cord or to the tunica vaginalis. The origin and significance of these adhesions have been the subject of much speculation. They have been ascribed to the persistence of folds of peritoneum normally present in fœtal life; or as the result of fœtal peritonitis, the frequency of which is upheld by Virchow, B. Schmidt, Orth and others; to the persistence of certain fibres of the gubernaculum; and they have also been considered as of post-hernial origin. There seems to be little doubt that in some of the cases these adhesions, by uniting the appendix to the migrating structures, have enabled the same forces which bring about the descent of the testicle to also play an active part in causing the descent of the appendix into the inguinal canal.

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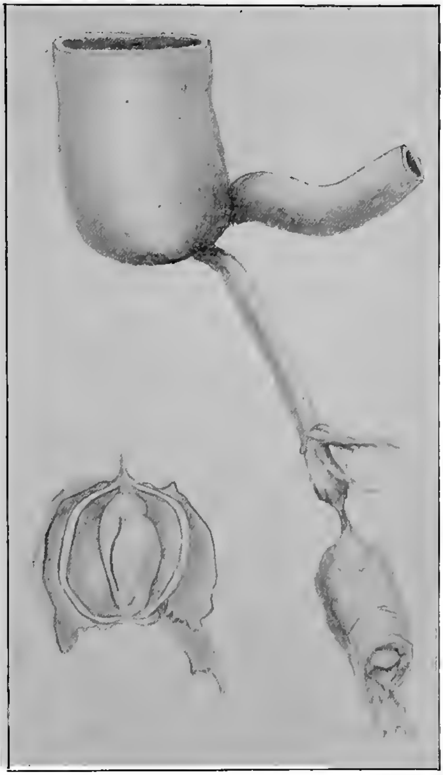
* Previously published in briefer form in the *Archives of Pediatrics* (March, 1904) to which journal we are indebted for the use of the accompanying cut.

In support of the view that these attachments may originate in fœtal folds of the peritoneum may be cited the fact that previous to the descent of the testicle into the inguinal canal the peritoneum overlying the testicle encloses it and forms a mesentery, the mesorchium, which also encloses the gubernaculum and forms two folds, one above the testicle and the other below it. The one below the testicle encloses the lower part of th gubernaculum, and is known as the *plica gubernatrix;* the one above the testicle is not constant, but when present usually covers the spermatic vessels and is known as the *plica vascularis.* Hutchinson states that at the time the testicle passes into the inguinal canal this ascending band or ridge of peritoneum can be found in about ten per cent. of all cases: its upper attachment varies; usually it is to the under surface of the mesentery of the lower end of the ilium, less commonly to the cæcum or vermiform appendix. A similar band is much more frequently found in females (fifty per cent. of all cases, according to Hutchinson), in whom it persists as the well-known appendiculo-ovarian ligament. The presence of this band with rigid superior attachments has been given as a cause of incomplete descent of the testicle.

As is well known, the testicle develops opposite the second or third lumbar vertebra, from which point it descends during the third month, by the end of which time it has reached the internal ring. It remains in this position until near the close of gestation or, according to some authors, enters the processus vaginalis as early as the middle of the seventh month. The position of the appendix is high in the abnominal cavity until the descent of the cæcum, which occurs about the sixth month, but, owing to the relatively great length of the appendix in the fœtus (eleven millimetres in each of two twelve centimetres fœtuses examined by us), it is at all times capable of coming in contact with the peritoneum covering the testicle. It is thus seen that inflammatory

To Illustrate the Article by Drs. Stanton and Shaw on "Infantile Inguinal Hernia of the Vermiform Appendix."

Albany Medical Annals, August, 1904.



conditions occurring in either the appendix or the testicle could result in the formation of adhesions between the appendix and the migratory peritoneum covering the testicle, and thus cause the descent of the appendix along with the testicle.

The following case, occurring in the service of one of us (Shaw) at the Albany Orphan Asylum, is of interest in that it represents a case of congenital hernia of the appendix, in which the descent of the appendix into the inguinal canal was undoubtedly caused by an early inflammation which involved both testicles, together with their peritoneal covering, and which resulted, we believe, in the formation of an adhesion between the distal end of the appendix and the tunica albuginea overlying the head of the right epididymis.

Sidney P., born November 10, 1902; admitted to the Albany Orphan Asylum January 31, 1903; died October 29, 1903. While under observation in the Asylum there were no symptoms referable to the appendix or genital organs; the patient dying of broncho-pneumonia following measles.

The following notes are from the autopsy protocol (Stanton):—

Abdomen—Abdomen is free from fluid. Omentum contains very little adipose tissue. Serosa smooth and glistening. Appendix is eight centimetres long and extends directly downward with free meso-appendix from caecum through internal ring and inguinal canal and is so united by adhesions to the testicle that the latter can be drawn up into the inguinal canal by traction on the appendix.

When the testicle is in normal position there is a slight evagination of the peritoneum around the appendix at the right of the internal ring; otherwise the funicular process is completely obliterated and there is no evidence of a hernia sac.

On dissecting out the appendix it is found that the portion lying within the canal is covered with a loose areolar tissue while a thick band of firm fibrous tissue unites the tip of the appendix to the tunica albuginea overlying the head of the epididymis.

Testicles—The parietal and visceral layers of the tunica vaginalis of both testes are distinctly thickened.

Anatomical diagnosis—Bilateral broncho-pneumonia. Cloudy swelling of liver and kidney. Acute congestion of spleen. Congenital hernia of appendix with adhesions between epididymis and appendix. Chronic bilateral peri-orchitis.

Microscopic examination—Sections from the left testicle show extensive thickening of the capsule and a growth of fibrous tissue between the tubules.

Microscopic diagnosis—Broncho-pneumonia; endothelial hyperplasia in spleen and retroperitoneal hemolymph node. Albuminous and fatty degeneration of liver. Slight albuminous degeneration of kidney. Atrophied thymus. Cloudy swelling of heart muscle. Chronic orchitis. Chronic periorchitis.

Explanation of illustration—The larger drawing shows the parietal peritoneum becoming continuous with the peritoneum of the appendix at the point where the appendix entered the inguinal canal and the band of fibrous tissue uniting the tip of the appendix with the tunica vaginalis. The smaller drawing is from a section through the tunica vaginalis showing the thickening of the parietal portion and the relation of the adhesion to the tunica vaginalis and the head of the epididymis.

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A STUDY OF THE CHANGES OCCURRING IN THE ENDOMETRIUM DURING THE MENSTRUAL CYCLE.

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Probably the first recorded observations on the condition of the uterine mucosa during menstruation were published by Kundrat and Engelmann in 1873. Since that time numerous investigators have studied the subject but the results of their work show the greatest differences of opinion.

Without doubt, as we shall see, these varied views were due to several causes, principally the source of the material and the more accurate results obtained through better preserving fluids and more satisfactory fixing methods as well as to the recent rapid progress in microscopical studies.

In the study of the changes which take place in the uterine mucosa during the menstrual cycle we have several methods to pursue. The first method employed was that of the examination of the mucosa in uteri removed at autopsy and consequently, as this was the most natural source for the securing of material for microscopical study, we find that the earlier and the greater number of observers, Kundrat, Englemann, Sir John Williams, Sinety, Leopold, Wyder, Von Kohlden, Christ, and Wendeln conducted their studies on the uteri removed at autopsy from patients who had died during menstruation.

That the earlier observations were faulty is not to be wondered at since it is a well-known fact that autopsy material unless secured very early post mortem is more or less changed. Gebhard referring to the conclusion of Wendeln obtained by the study of autopsy specimens, claimed that it is never allowable to show cadaveric preparations as proof of the condition of the mucosa where the material has been taken thirty-four hours post mortem. We believe that even this is rather late to secure proper material.

In the first place, as pointed out particularly by Leopold and Wyder, it is absolutely necessary that an exact anamnesis be secured in each case, whatever the source of the material, in order to be assured that one is dealing with a true menstrual hemorrhage. That this has not been followed in many of the earlier observations is certain.

Another source of error in the earlier observations, and one that is liable to be experienced by every laboratory worker unless the greatest care is taken, is that in passing the material through the fixing solutions there may be more or less loss of substance. Inasmuch as the first important question to be decided is whether there is a loss of substance resulting from menstruation or not, it is necessarily important to use such fixing solutions as will preserve the specimens intact.

A number of authors have not stated their methods of preserving and fixing their material. A number employed Müller's fluid. Leopold preserved his specimens first in weak then in stronger alcohol. He was opposed to Müller's fluid because the superficial layers which are saturated with blood are easily broken off. This is certainly true unless the specimens are most carefully handled, and it is due to the fact that Müller's fluid must be changed and the specimens washed so often before the tissue is fixed. After hardening has taken place the pieces of tissue may then be moved about and the fluids changed frequently without loss of substance. Mandl finds that the corrosive sublimate solution proves the best for the study of the condition of the epithelium and that Flemming's fluid was of the greatest service for the study of the process of regeneration.

Finley and other recent observers used Zenker's solution and since this fixes the specimens quickly without changing the solution and without handling them frequently it has proved very satisfactory. Could this solution have been used in earlier observations there would have been less disagreement as to the changes which take place especially as regards the loss of substance.

Möricke was the first to examine scrapings from the normal menstruating uterus and thus excluded the possibility of postmortem changes. Lëhlein, Gebhard, Westphalen and others soon followed his example and these investigators arrived at different conclusions than did the earlier observers who used autopsy material. Wendeln had some doubt of the value of the examination of curettage specimens on the grounds that the whole mucous membrane is not obtainable and consequently conclusions based on the examination of only a part should not be made. It is possible, too, that curetted material may appear hemorrhagic on account of the numerous blood cells which are intimately associated with the material in its removal and in the process of blocking.

Sinety examined the menstrual flow and the mucus adhering to the superficial layer of the mucosa in order to draw conclusions as to the condition of the deeper layers. In such a method the possibility of arriving at erroneous conclusions is apparent. Wyder aspirated the menstrual discharge from the cavity of the uterus by means of a uterine syringe in order to avoid the glands of the cervix and to reduce the negative pressure to a minimum.

In order to determine the probable loss of substance of the mucosa during menstruation the writer undertook to examine the napkins of thirty patients through the menstrual period. The patients were instructed to change the napkins frequently and to soak in cold water, being careful to save any clots and at the end of menstruation to take a vaginal douche of plain cold sterile water so that all the discharge might be collected. This douche water and that in which the napkins were soaked was centrifuged so as to obtain all the sediment possible. This sediment was then hardened in alcohol and passed through in the routine manner. Great care was taken to secure patients who had a normal menstrual history and in whom there was no apparent diseased condition of the endometrium.

The small amount of material thus obtained was cut and stained with hæmatoxylin and eosin. The result of such examination will be mentioned later on.

Another method which is the most important of all is that of the examination of sections of uteri removed during the menstrual period for lesions not involving the endometrium. This method of examination was only lately carried out since surgeons prefer not to remove the uterus during active menstruation.

Probably the most elaborate investigations were carried on by Gebhard, in Berlin, and Westphalen, in Keil, who not only studied the mucosa of menstruating uteri obtained by curettment and of uteri obtained at autopsy but also sections of uteri removed by operation during the menstrual period. Williams, Findley, Edgar and others in this country also recorded their observations on the examination of the mucosa of uteri removed during operation.

In women, who must lose diseased adnexia and in whom the anamnese and the examination of the uterus led one to expect no particularly abnormal condition of the uterine mucous membrane, Mandl and other operators awaited menstruation and removed the uteri during this period. No intra-uterine manipulation was carried out and in order to protect the organ from unnecessary handling extirpation was performed as quickly as possible by clamping off the parametrium and ligaments and cutting rapidly. In order to avoid the slightest possible injury to the mucosa the uterus was opened on the anterior wall cutting from the cervix to the fundus and then a portion was removed from the posterior wall and placed immediately in fixing fluids. Findley placed the uterus in salt solution immediately after removal and then placed in Zenker's solution for twenty-four hours.

The views of the numerous investigators are so contradictory on several points that it will be necessary to consider them more in detail.

Leopold divides the menstrual cycle into four stages: (1) active menstruation; (2) regeneration; (3) resting stage; (4) premenstrual swelling.

In as much as the stage last mentioned is really the preparatory one, according to my observations, and the beginning of the phenomena exhibited in the change of the uterine mucosa due to menstruation, we will discuss this division of our topic first.

Westphalen, Leopold, Doléris, Pompe, Van Meerderwordt, Herzog, and others are practically agreed with the conclusions of Gebhard based on his observations of the scrapings and sections of uteri removed during the menstrual period for lesions not involving the endometrium.

From a study of the literature on the subject, and from the examination of such material as I have been able to secure, the following information has been gleaned.

In this stage, which begins to develop gradually as soon as the process of regeneration is complete, which is about the eighteenth day after the flow ceases, we find that the capillaries of the mucosa are congested resulting in a serous or serosanguineous exudate infiltrating the stroma of the mucosa. During the state of regeneration the cells of the stroma lay over each other rather thickly but now become pressed apart particularly in the outer third of the mucosa.

The protoplasm of these cells become compressed and the projections by which they are bound together are either greatly lengthened or completely separated. In the meshes lies a light opaque mass, which seems similar to blood serum and which is often separated in the larger vessels from the chromocytes.

Later the blood leaves the capillaries and infiltrates the stroma, gravitating in the direction of least resistance, *i. e.,* toward the uterine cavity, and, just before the active flow begins, forming a collection of blood beneath the surface epithelium—the sub-epithelial hæmatoma of Gebhard.

It is quite impossible to say whether the bloody condition of the effusion along the borders of the mucosa belongs entirely to the normal or not, for it is apparent that in curettage hemorrhage easily occurs in the mucosa while in extirpation an engorgement of the vessels occurs very easily, especially when the broad ligament is not clamped. Even traction on the uterus from below, according to Westphalen, results in venous stasis with consequent small hemorrhages.

The vessels become larger in the loosened swollen stroma and are for the most part more filled than in the period of regeneration but the greater increase in size occurs only shortly before the beginning of menstruation proper.

Many observers agree that there is also an increase in the size of the glands of the mucous membrane, since these appear widened and winding and frequently on cross section the walls seem to be thrown into folds in the lumen. The increase in size of the glands is due, no doubt, to the collection of the secretion of the gland cells. It is this mucous-like product of the gland cells which gives them quite a granular appearance. The gland cells become uniformly swollen and take stains more evenly, and their nuclei are more widely separated as a result of the increase in the volume of the protoplasm, and are uniformly more round in comparison to the oval-nuclei which are seen in the regeneration period. In all the stages the cell nuclei are near the base as a rule, although Westphalen has often noticed that they stand in the middle of the cell in the beginning of the state of pre-menstrual swelling. Consequently the mucosa is increased in thickness from two to three millimetres up to six and seven millimetres,—the thickness varying greatly in the same uterus owing to the unequal distribution of the muscle layers directly beneath the mucosa.

Kundrat and Englemann found a fatty degeneration of the mucous epithelium as well as of the gland cells and interglandular tissue and the hemorrhage and œdema of the mucosa according to these early investigators, were produced by a fatty degeneration of the walls of the vessels which were now increased in size and completely filled with blood—these conditions resulting in a laceration of their walls and a consequent hemorrhage into the tissue. They noticed that the greater part of the hemorrhage was superficial and that fatty degeneration is most noticeable in the same portion of the mucosa.

Sir John Williams also believed that fatty degeneration occurred and consequent degenerative changes took place.

Leopold claimed, and rightly, that the hemorrhage is a superficial capillary one due largely to the peculiar condition of the vascular structure in the mucosa (numerous arteries and capillaries and proportionally a less number of veins). What he described as a fatty degeneration of the superficial elements, was assigned, not as the previously mentioned observers assigned as the cause, but as the result of the hemorrhage.

Möricke and other observers maintain that fatty degeneration of even the slightest grades is not to be found.

Kundrat, Sinety, Leopold, and others have described an increase of the round cells and small celled infiltration but this is not confirmed by subsequent observers and their presence is denied by others.

Leopold described the appearance of giant cells (with eight to ten and even more nuclei) especially in the projections of the mucosa into the muscular tissue. Other investigators have confirmed this observation.

At the end of the pre-menstrual stage we find, therefore, the mucosa is swollen greatly and infiltrated with a serous or serosanguineous exudate and that collections of blood are formed beneath the surface epithelium ready to burst out.

The stage of active hemorrhage now appears—being described as the first stage by Leopold and as the second by Gebhard. The question now arises as to how the blood reaches the uterine cavity and how much mucous tissue is destroyed by this process.

Gebhard states that the blood reaches the uterine cavity by being forced between the epithelial cells of the surface or of the glands, or the continuity of the surface is broken by the lifting of small masses of cells from their bed these providing an exit for the collections of blood beneath.

Christ believed that in the weaker menstrual congestion the

To Illustrate Dr. Lipes' Article on "A Study of the Changes Occurring in the Endometrium during the Menstrual Cycle"

Albany Medical Annals, January, 1904.

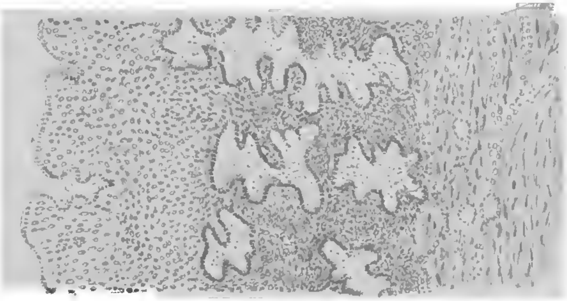

FIGURE 1.

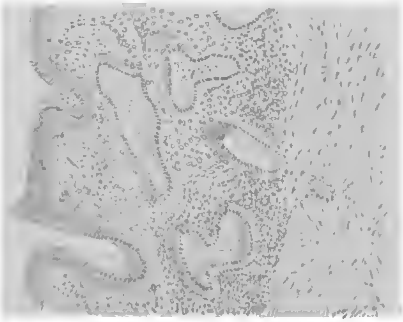

FIGURE 2.

blood escaped between the epithelial cells of the surface of the mucosa and of the glands. Where the congestion was more marked slight defects occurred in the surface through which the blood poured out and where the menstrual flow was very profuse there was a more sudden and a greater loss of the surface epithelium, which allowed the outflow of blood. This observer claimed to have seen in many places the passage of red cells between the superficial epithelium as well as between the epithelium of the glands but he has given us no drawings of this condition. Others agree with this view but do not make the statement as a result of their own observations.

Mandl made careful examinations of a number of sections but did not observe in any case the passage of red blood cells between the epithelium although these cells are easily observed when specimens are fixed in sublimate solution and stained in hæmotoxylin and eosin—the method is adapted. He repeatedly found leucocytes, however, which had become fixed in their wanderings between the epithelium of the surface and of the glands as well, and believed that by the wandering of these leucocytes the union of the epithelial cells is broken so that the blood follows more easily in such places.

But perhaps the most important question, and the one concerning which there is the greatest diversity of opinion, is whether or not any portion of the mucosa is destroyed by the process of menstruation.

If we examine the results of the studies of the various authors already mentioned we will see that the earlier observers particularly held the opinion that not only is the whole superficial epithelial layer destroyed but also a considerable part of the mucosa disappears.

Another group of observers believe that the whole mucosa and even the superficial epithelial layer remains intact; while a third group takes the middle ground and describes a loss sometimes of a less, sometimes of a greater part of the epithelium and mucous membrane.

In the first group we find Engelmann, Kundrat, Sir John Williams and Von Kahlden. The latter, who undertook a through study of the published communications on this subject up to the appearance of his work in 1889, came to the conclusion that in all probability in menstruation the whole surface epithelium with a very considerable part of the mucosa is thrown off. But these observations were made on cadaveric material which had been obtained when post-mortem changes had probably taken place and the fixing solutions used necessitated frequent changes and consequently much handling. As already pointed out these conditions would result in a loss of substance in such frail material as the uterine mucous membrane, especially during menstruation.

Of the group of men who believe that at no time during menstruation is any part of the mucosa lost, De Sinety is the only early worker on autopsy material. Möricke, Strassmann, Findley, J. Whitbridge Williams, C. Ruge, Veit, Gebhard, Mandl, Leopold, J. Clarence Webster, Meerdervoort and others believe that only a small portion of the superficial epithelium is lost and that this is purely accidental.

Underhill, Wendeler, Heape, and others, believe that only the superficial portion of the mucosa is destroyed.

There is no doubt but that the character of the hemorrhage has much to do with the amount of destruction of the superficial epithelium. If the congestion is of rapid development and the collection of blood beneath the surface epithelium is extensive there must necessarily follow a destruction of at least a portion of the overlying surface epithelium. If the hemorrhage is slight and takes place largely by diapedesis the loss in the epithelium would be almost nil.

This I have proved, at least to my own satisfaction, by the examination of the menstrual discharges as already mentioned. Lack of space will not allow a detailed description of these cases.

In the thirty cases examined the period of menstruation extended from one to eight days. There were two cases of one day's duration, one of two days, twelve of three days, seven of four days, three of five days, two of six days, two of seven days, and one of eight days' duration, all of which were carefully examined.

In the first three cases mentioned there was practically no sediment and this was composed principally of red-blood cells and some vaginal epithelium. In two of the twelve cases where the flow lasted three days the onset was severe and the flow considerable, but with little or no pain experienced by the patient. In these two cases there was considerable sediment which contained a large amount of blood and numerous epithlial cells from the mucosa, as well as vaginal epithelium and other debris.

In one of the seven cases menstruating four days, the flow was slight the first day but increased in severity the last three days. In this case, however, there were not many epithelial cells found in the discharge. In the two cases of six days, the two of seven days, and the one of eight days' duration the flow was considerable in amount as it extended over so many days but it occurred gradually. Proportionately to the amount of sediment there was a less number of epithelial cells than in the two specimens obtained from the patients whose periods lasted three days.

In as much as only practically normal cases had been selected the results show that there is some loss of epithelium during normal menstruation and that the amount of loss is dependent upon the severity and not necessarily upon the length of the menstrual period. There were certainly not enough epithelia in the discharge in any of the cases to suggest a complete loss of the superficial layer of the mucosa.

With the disappearance of the mentrual flow involution begins. We find that the blood vessels decrease rapidly in size as the engorgemnt lessens and that blood is no longer extravasated into the connective tissue spaces. What blood is left in the stroma is rapidly absorbed.

Granting now that there is a partial loss of the surface epithelium the question arises as to how this loss is repaired.

According to Leopold the surface epithelium which has been lifted from its bed, if the continuity has not been broken on all sides, resumes its former place and the lost epithelium is regenerated from adjacent cells. This is the consensus of opinion.

Sir John Williams, who claimed that the whole mucosa was destroyed, believed that the mucous membrane was regenerated from the epithelium of the glands which penetrated the muscle layer. Wyder, who taught the partial destruction of the mucosa, believed that there was a cell hyperplasia of the interglandular tissue in the deeper layer of the mucosa, which provides for the restoration of the loss of cells and that a regeneration of the superficial epithelium takes place from the gland epithelium and from the remaining " cell-islands."

Wendeler believed in a partial loss of the epithelium and that the necessary regeneration was accomplished as previously from a cell membrane situated under the base of the old epithelium containing flat, tender epithelium. No other investigator has observed such a membrane, however.

Mandl was the first, I believe, to demonstrate the various stages of well marked mitosis in the epithelium of the covering layer and showed that the lost cells were replaced by indirect cell division of the remaining cells. He believed that the gland cells also assisted in this process but did not agree with Von Kahlden who claimed that the formation of the new cells resulted entirely from those of the gland whose openings became widely extended and whose cells spread out in all directions.

The length of time necessary for the complete regeneration of the mucosa varies necessarily according to the amount of tissue lost. Williams believed that the entire mucous membrane was restored in a few days. Leopold states that the regeneration of the lost epithelium is performed likewise in a few days after the close of the menstrual flow. Westphalen, however, thinks that this process is a longer one consuming from six to eighteen days and believes that this stage is prolonged through the third or resting period as described by Leopold. In any event the interval between the complete restoration of the mucosa and the premenstrual congestion state is very short.

Whether the mucous layer of the Fallopian tubes undergoes a change during menstruation is a question. Personally I have not been able to examine the mucosa of the tubes removed during menstruation.

Mandl in one case, where he had removed the uterus and adnexia on the fourth day of menstruation, found that the mucous membrane of the tubes was swollen and hemorrhagic although the adnexia were normal.

Findley is the only observer who has exhibited a drawing of the mucous membrane of the tube during menstruation. He reports two cases in which the changes in the mucosa of the tubes were similar to those in the uterus, *i. e.*, there was a marked engorgement with blood, and free blood was found in the mucosa and in the lumen of the tube. The surface epithelium was found intact.

In conclusion we would offer the following resumé:

The menstrual cycle is divided into three periods; the first, preceding the menstrual flow and characterized by gradual development of a capillary congestion resulting in a serous or serosanguineous infiltration of the stroma of the mucosa, separating the cellular elements and gravitating toward the periphery forming collections of blood beneath the surface epithelium. Slight glandular hypertrophy as well as a swelling of the gland cells takes place, with a consequent hypertrophy of the whole mucosa. This stage is well exhibited in figure I, taken from a drawing by one of my students, Mr. Harry Rullison, to whom I would express my indebtedness, of a section of uterus removed immediately preceding the menstrual flow. A capillary engorgement and infiltration of the stroma, separating the cellular elements is especially noticeable in the outer portion. The enlarged cork-screw-like glands suggest a mild form of glandular hypertrophy.

The second stage of active hemorrhage is characterized by an outflow of blood through a diapedesis or through a rupture of the sub-epithelial hæmatoma, with more or less loss of the superficial epithelium depending largely upon the severity of the process. Figure II, a drawing of a section of a uterus removed the first day of the menstrual hemorrhage shows the infiltrated area near the surface with a breaking in the continuity of the surface epithelium allowing the blood an exit. In this plate the mucosa is drawn relatively too norrow.

In the third stage involution takes place. The engorgement of the blood vessels becomes quickly lessened and a rapid absorption of the blood in the stroma takes place. The epithelium which has been lost is regenerated by indirect cell division of the adjacent cells. This stage is prolonged until the premenstrual swelling begins or there is a slight interval during which the mucosa is inactive.

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THE ISLANDS OF LANGERHANS IN CONGENITAL SYPHILITIC PANCREATITIS.

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It is not my purpose in the present communication to give a detailed study of the lesions of congenital syphilitic pancreatitis. The condition is not important clinically, for it is found usually only in the still-born or in those dying shortly after birth; the pathology of the condition on the other hand, has been thoroughly studied and little can be added to the original description of Birch-Hirschfeld and the later systematic study of Schlesinger. The histological picture, however, shows a peculiar relation between the islands of Langerhans and the newly formed tissue which, as it has not been generally recognized and as it offers evidence in confirmation of our newer ideas concerning the anatomical and physiological independence of these structures, is I believe, worthy of special consideration. The study of the islands in this condition is also important, because occurring as it does in the foetus, it offers an opportunity to study the structures under adverse conditions of development, thus filling the gap between the normal development and the pathological changes seen in the adult organ.

Our recently acquired knowledge of the islands is almost entirely due to the work of Opie,[1] who has shown that a certain proportion of the cases of pancreatic diabetes have a definite relation to lesions of the islands of Langerhans. Upon these observations, which have been confirmed by several American and German investigators, is based the assumption that the islands have a physiology distinct from the remainder of the pancreas, and concerned especially with carbo-hydrate metabolism, therefore of prime importance in the pathology of diabetes. Very substantial support of this anatomical and physiological independence is offered by the experiments of Ssobolew[2] and Schulze.[3] These investigators, working independently, have shown that after ligation of the pancreatic duct in animals, the glandular portion of the organ atrophies and is replaced by fibrous tissue while the islands are unchanged and the urine remains free from sugar. Opie has observed a similar condition in the pancreas of man as the result of partial or complete duct obstruction by calculus or cancer.

It is this same picture of a chronic sclerotic inflammation with disappearance of the greater portion of the glandular structure and the persistence of the islands that is seen in the congenital luetic lesion of the pancreas. This persistence of the islands has not, however, been generally recognized, owing probably to the infrequency of the post-mortem examination of newly born children and in part to the fact that our interest in the pathology of the island has only recently been aroused. Previous to this awakening the only references are those of Schlesinger[4] and Condon[5] who merely mention the presence of the islands; while, since, Opie and Ssobolew the chief supporters of the theory of anattomical independence have offered this persistence of the islands as evidence in support of their view. At the time of their publications, however, our knowledge of the normal development of the islands was incomplete. This gap has been filled by my recent study[6] of the development of the island in the human embryo, and it is in connection with the results of this study that I wish to consider the changes in the syphilitic organ.

Literature of Congenital Syphilitic Pancreatitis. The first complete study of luetic pancreatitis of the new born was made by Birch-Hirschfeld[7] in 1875. In the series then reported, lesions of the pancreas were found in thirteen of twenty-three cases examined, but in a later series, in but twenty-nine of one hundred twenty-four. The frequency of the lesion in the second series agrees with the observations of subsequent writers.

The gross appearance of the organ is characteristic, the most striking feature being the increase in consistence, which in advanced cases approaches that of cartilage. An increase in size and weight is also quite constant. On section the surface of the organ is hard, white and glistening, the glandular appearance being entirely effaced. Birch-Hirschfeld compares the appearance on section to that of a fibroid; Cruveilhier, to that of a scirrhus cancer. Previous to Birch-Hirschfeld's study, this induration of the pancreas in congenital lues had been noted in isolated instances by Osterloh,[8] Cruveilhier,[9] Hecker,[10] Œdmansson[11] and Wegner.[12] The changes are most marked in the head of the pancreas, a fact which led Mraczek[13] and Beck[14] to consider the lesion to be an extension from the duodenum. Schlesinger states that there is no constant relation to syphilis of other organs, though the pancreas may be adherent to such.

Birch-Hirschfeld (1875) describes the lesion, histologically as an increase of connective tissue which compresses and causes atrophy of the glandular elements, without evidence of degeneration. Schlesinger (1898) gives a most complete histological study and decides that the increase of connective tissue is of perivascular origin. Contributions to the pathology of the lesion have been made also, by Huber,[15] Friedreich,[16] Mraczek, Müller,[17] Baumgarten,[18] Beck, Heubner,[19] Ssobolew, Opie and Condon. Gummata have been found only by Klebs,[20] Beck and Birch-Hirschfeld which is in striking contrast to the syphilitic lesion of the adult pancreas. Baumgarten and Cruveilhier describe a lardaceous appearance, but whether they use this term in the descriptive sense or to specifically refer to amyloid infiltration, is not clear from the text. Some difference of opinion exists concerning the period at which the lesion develops. Birch-Hirschfeld places it late in pregnancy; Schlesinger much earlier and quotes cases described by Müller and Mraczek in which it existed at the fifth month. Opie's statement that the almost complete absence of glandular tissue is due to arrested development rather than to degeneration indicates that he favors Schlesinger's view. It may be mentioned that the condition has been found five months (Birch-Hirschfeld) and three and a half years (Heubner) after birth. The involvement of the pancreas occurs in order of frequency after that of bone, lung, spleen and liver.

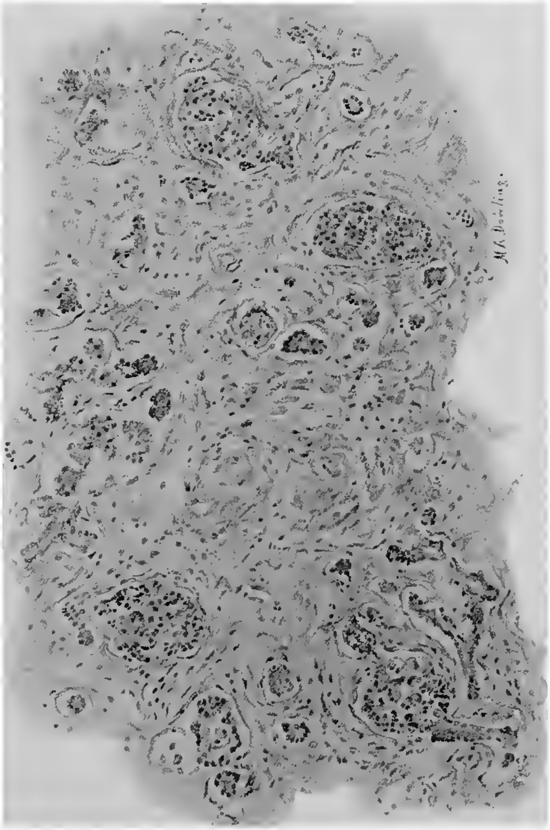
Material. My interest in congenital syphilitic pancreatitis was first aroused by Prof. Marchand of Leipzig, at whose suggestion I undertook an investigation of several minor points concerning the development and pathology of the islands of Langerhans. From the material of the Leipzig Institute, six specimens were obtained. Later while completing a study of the embryology of the islands, with the aid of material placed at my disposal by Prof. Mall of Baltimore, two additional examples were found. A single specimen was obtained from Dr. Flexner's collection of pancreas material and one also from the collection of Dr. George Blumer. I take this opportunity to thank these gentlemen for placing this unusual material at my disposal.

In all of these ten specimens the lesion is of the advanced sclerotic type with almost complete disappearance of the glandular elements. The early stages with infiltration of plasma and lymphoid cells are not seen. A careful study of the lesion adds practically nothing new to our knowledge of the general process. Selective stains prove the new tissue to be mainly of the white fibrous variety; the elastic tissue to be unchanged, or indeed in some instances, less in amount than in the normal pancreas. In one case very widespread mucoid degeneration of the new connective tissue was seen. Miliary gummata (syphilome miliare) were found in but one of the ten specimens.

The most striking feature is the persistence of the islands of Langerhans, despite the general destruction of the glandular acini. Throughout the dense fibrous tissue, with here and there the fragmentary remains of gland tissue, the islands stand out prominently, often surrounded by denser whorls of investing stroma, but apparently uninjured. (See illustration.) This

To Illustrate Dr Pearce's Article on "The Islands of Langerhans in Congenital Syphilitic Pancreatitis."

Albany Medical Annals, January, 1904.



appearance is present constantly in all specimens and in all grades of the lesion, and the most careful search fails to reveal, in the islands, evidence of degeneration or atrophy, or the ingrowth of connective tissue. The absolute resistance of the islands to the process so destructive to the secreting portion of the gland is very strong evidence in favor of their anatomical independence and this condition, if considered in connection with our knowledge of the development of the islands, is very readily explained. While in most instances the islands appear entirely isolated, close examination shows that occasionally an island is connected with a glandular acinus by a stalk-like process of cells. This connecting band is in most instances a solid mass of epithelial cells; though, sometimes, a semblance of a lumen may be discerned. Opie alone, as far as I am aware, notes this band of cells connecting island and acinus. Upon this observation and the fact that no evidence of degeneration is seen in the island he bases the assumption that the island in its early development is in connection with the acinus and that its development is interrupted, in syphilitic pancreatitis, by the ingrowth of connective tissue which causes atrophy of the glandular tissue and leaves the more resistant island in its undeveloped state. At the time of Opie's communication our knowledge of the development of the islands was incomplete and especially so the manner in which the island became independent of the acinus from which it originated. That his assumption is correct, however, is shown by the results of my recent study of the development of these structures in the pancreas of the human embryo. These results may be briefly summarized as follows:

"The islands of Langerhans (embryo of fifty-four millimetres), originate through a proliferation and differentiation of the cells of the primitive secreting tubules. The differentiated cells characterized by a rich, finely granular, eosinophilic protoplasm lie as small round or oval masses in direct continuity with the cells of the tubule. Later, (embryo of about the third month) the attached portion becomes constricted, and lengthening, forms a a stalk-like, solid process of cells connecting the island with the acinus. At this period, a few entirely isolated islands are present. A separation takes place apparently brought about by the pressure of the investing connecting tissue. Vascularization has now occurred. In still later stages a progressive vascularization, increase of cells, arrangement of the cells in columns, and appearance of a fine reticulum is observed. The rapidly forming glandular structures finally surround the islands which then occupy the centres of the lobules."

From this summary it will be seen that in the pancreas of the third month the islands are still connected with the acini by solid processes of cells. The proportion of connective tissue at this time is very great, as the rapid glandular growth does not occur until the fifth and sixth months. Any disease of the pancreas occurring at this time would, therefore, influence the development of the organ, and evidence of this faulty development would be present at any subsequent stage of the lesion.

This seems to be the case in the lesion under consideration. Syphilis of the pancreas has been observed as early as the fifth month (Müller) and although there are no definite observations of its earlier occurrence, the appearance of the islands in the luetic pancreas when compared with the normal development of these structures indicates the possibility of the lesion occurring as early as the third month. The general microscopic picture of the normal pancreas at the end of the third month is very similar to the syphilitic organ at the sixth or seventh month, except that the latter has a larger proportion of connective tissue: *the same stage of development of the islands is seen in both.* In other words, at the latter period we have the development of the third month plus the connective tissue produced by the syphilitic lesion. It seems justifiable, therefore, to conclude that the syphilitic infection occurs at the period (third to fourth month) when the islands are still connected with the gland tubules, and that the newly formed tissue causes atrophy of the gland acini, but spares the more resistant islands. Thus is explained the similarity of the islands in the two conditions. The ultimate factor in this resistance of the islands is their abundant blood supply. That this vascularization of the island is not altered in syphilitic pancreatitis, I have demonstrated by the study of the diseased organ injected with Berlin Blue.

The evidence obtained by experiment and by the study of the pancreas of diabetics has already placed the theory of anatomical independence of the islands upon a substantial basis. The study of their development, has demonstrated that although they originate from the glandular tissue they eventually become wholly independent structures anatomically. It is with the object of adding still further confirmatory evidence, that this communication which adds nothing essentially new, but attempts to correlate known facts, is made.

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CANCER OF THE PANCREAS AND GLYCOSURIA.*

(*A Histological Study of the Changes in the Islands of Langerhans*)

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This investigation was undertaken for the purpose of determining what relation, if any, the islands of Langerhans may have to the glycosuria occasionally seen in connection with cancer of the pancreas. That pathological changes in these structures are frequently associated with diabetes has been satisfactorily demonstrated by the investigations of Opie[1] and others, and has led to a more definite knowledge of a form of diabetes which may properly be called pancreatic diabetes. No attempt has been made on the other hand, as far as I am aware, to demonstrate the presence of similar changes in connection with the glycosuria occasionally associated with cancer of the pancreas. That some of these changes—hyaline degeneration, chronic interacinar pancreatitis involving the islands and, according to a few investigators, diminution in the number of the islands—might result from the involvement of the organ by cancer is evident from our knowledge of the secondary lesions frequently accompanying such invasion. It is well known that duct obstruction, frequently the result of cancer of the head of the pancreas, readily causes a chronic pancreatitis; and it is possible also that the destruction of a large portion of the pancreas parenchyma by the new growth may destroy the islands to such an extent that they are no longer equal to the demands made upon them.

On the other hand we have no adequate explanation of those cases in which, though the pancreas is extensively or completely replaced by the new growth, diabetes does not exist.

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Such complete destruction, as in the cases reported by Litten[2] and v. Hansemann,[3] is analagous to the extirpation experiments by v. Mering and Minkowski,[4] but the absence of glycosuria is opposed to their results. v. Hansemann has attempted to explain the discrepancy by assuming that in primary cancer of the pancreas the tumor cells originating from pancreas parenchyma inherit the function of internal secretion peculiar to the normal cell. This explanation, however, is entirely hypothetical and in the light of our present knowledge of pancreatic diabetes loses its force unless we assume that all primary cancers of the pancreas arise from the islands of Langerhans, which, despite the recent publication of Fabozzi[5] supporting such origin, appears most improbable. If our newer theories concerning the relations of the islands to carbohydrate metabolism are firmly grounded, we should expect to find evidence of the persistence of the islands in such cases. With these various possibilities in mind, I have made a careful histological study of thirty cases of cancer of the pancreas, in three of which glycosuria was present.

The literature offers but scanty information concerning the frequency with which glycosuria occurs in connection with cancer of the pancreas. Such cases are not uncommonly reported but without reference to the occurrence of cases not complicated by glycosuria. From a hasty review of the subject, I believe the proportion (one in ten) shown by my cases to be high. We have, however, definite information concerning the reverse condition, that is, the frequency of cancer of the pancreas in connection with all forms of diabetes. In Oser's[6] series of 188 cases of diabetes, cancer occurred in 24; in Williamson's[7] series of 23, once; and in 139 cases reported by Windle,[8] in three. v. Hansemann's[9] tabulation of 72 cases of diabetes with pancreatic lesion contains five cases of cancer. I have examined many of the original descriptions of the cases quoted in these series with the object of determining if any peculiar macroscopic or microscopic conditions existed. The task has been most unsatisfactory for many of the reports are of a clinical nature and gross and histological description are meagre or entirely lacking. This analysis, however, confirms the well known clinical fact that in the majority of cases the new growth is in the head of the pancreas and by duct obstruction causes an atrophy (chronic pancreatitis?) of the distal portion of the organ. This point is especially emphasized by v. Hansemann, Dieckhoff[10] and Windle.

The material upon which this study is based consists of the tissues from thirty cases of cancer selected from a group of thirty-five examples of new growth in the pancreas. As the material has been gathered from different sources, often from routine collections of autopsy material, it has not always been possible to procure tissues from the different portions of the uninvolved pancreas as well as from the cancerous portion, nor for the same reason, have essential data concerning clinical history and pathology been available in all cases.* Thus while all cases have been utilized in the study of the histological changes but twenty-one have been available, on account of incomplete examination of the urine, in arriving at conclusions concerning the occurrence of glycosuria. The thirty cancers studied may be classified as follows: primary in the head of the pancreas, nine; in other portions of the organ, 4; secondary to gall bladder or ducts, five; to stomach, eight; to breast, one, and to uterus, one. Glycosuria occurred in but three cases; in two of which the tumor was primary in the head of the pancreas; concerning the third, no clinical or pathological notes were available.

The results of the histological examinations, especially as concerns the islands of Langerhans are more readily described under the following headings: changes in (*a*) the immediate neighborhood of the new growth, (*b*) at a distance from the tumor, (*c*) in cases with extensive involvement, but no glycosuria, and (*d*) in cases accompanied by glycosuria.

(*a*) The important changes at the edge of the advancing cancer are the persistence and increase in size of the islands of Langerhans. While the glandular elements are invaded and replaced by the new growth and the newly formed connective tissue, the islands remain unaltered in the midst of the stroma, and occasionally, are even enclosed by a mass of tumor cells. Not only is this true of the edge of the tumor, but in the well infiltrated parts the islands may be seen in the stroma without remnants of acini. The increase in size of some of these structures is four or five times that of the normal islands. These giant islands are typical in structure and readily distinguished from small alveoli of cancer cells. They represent a true hypertrophy of the islands and not altered pancreas acini.

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*I take this opportunity to acknowledge my indebtedness to Prof. F. Marchand of Leipzig Dr. Ludwig Hektoen of Chicago, Dr. F. B. Mallory of Boston, Dr. James Ewing of New York, Dr. W. G. MacCallum of Baltimore, Dr. W. T. Longcope of Philadelphia, Dr. M. Herzog of Chicago, and Dr. George Blumer, who have kindly placed material at my disposal.

(*b*) The changes at a distance from the tumor depend apparently upon the location and size of the same. With a cancer of the head of the pancreas causing pressure upon the duct a chronic interstitial pancreatitis of severe grade always existed, which, with the exception of one case to be described later, was always of the interlobular type. The islands persist in the midst of dense connective tissue and are not invaded by it. This condition has been observed by Opie in several similar cases without glycosuria.

A tumor at the head of the pancreas not obstructing the duct does not cause chronic interstitial changes. Small tumors of any portion of the pancreas are unaccompanied by changes in the islands of the normal portion of the organ; on the other hand, if the new growth is of considerable size, definite hypertrophy of these structures is apparent.

(*c*) But two cases of diffuse involvement of the organ occurred in this series; in neither was glycosuria present. These are, however, not analagous to those discussed by Hansemann, for areas of normal pancreas could be found here and there, lying in the midst of the new growth. In such areas were large islands, several times the normal size.

(*d*) Three cases of cancer of the pancreas accompanied by glycosuria are included in this series. One of these could not be utilized in the present study because of lack of data; the gross description of the pancreas not being available and the histological study incomplete inasmuch as only the tumor had been preserved and a study of the uninvolved portion of the pancreas was therefore impossible. The second case, a primary cancer of the pancreas involving the head only and accompanied by a slight intermittent glycosuria with free fat in the stools, showed no changes in the uninvolved portion of the organ. The islands were few in number and the increase in size usually seen in the immediate vicinity of the new growth was not evident. The third case was one of cancer of the pancreas with advanced chronic pancreatitis of the interacinar type. Sugar had been present in the urine for several months before death. The entire length of the pancreas was fifteen centimetres; the proximal five centimetres occupied by the tumor, the remainder of the organ atrophied and indurated. Histological examination revealed a severe grade of chronic pancreatitis with small scattered groups of more or less altered acini. Within these, smaller strands of connective tissue had penetrated, involving to a varying extent, the islands of Langerhans.

While it is impossible to draw any definite conclusions from such a small number of cases, these observations are very suggestive and offer some support of the newer ideas concerning the anatomy and physiology of the islands. The persistence of the islands in the midst of the tumor stroma supports the theory of anatomical independence, an independence which I have recently definitely demonstrated by a study of their development.[11] This persistence is analagous to that described by Schlesinger,[12] Opie, Condon[13] and Pearce[14] in congenital syphilitic pancreatitis, and by Opie in various other sclerotic conditions of the organ. The increase in size of the islands suggests a purposeful enlargement due to increased function and therefore of the nature of a compensatory hypertrophy. A similar hypertrophy of these structures has been described by Warthin[15] and by Ohlmacher[16] in connection with cancer of the liver, and is considered by them, also, to be compensatory in nature, compensating, however, for the lost or limited liver function. The livers of my cases have not been available in all instances for histological examination, and I have not therefore been able to arrive at any conclusion concerning the relation of enlarged islands to lesions of that organ. It is possible that a relation of a compensatory nature may exist between the carbohydrate metabolism of the liver and the islands of Langerhans; but the hypertrophy of the latter structures when associated with cancer of the pancreas is, I believe, an attempt to compensate for the function of the lost islands.

The cases of diffuse cancer of the pancreas without glycosuria can be explained only on the supposition that the amount of normal pancreas remaining is sufficient to furnish the secretion necessary to carbohydrate metabolism. v. Mering and Minkowski found in their extirpation experiments that if one-fourth to one-fifth of the pancreas remained, diabetes did not result; a destruction of the pancreas by cancer we may consider analagous to partial extirpation. In both of my cases of diffuse cancer, small areas of pancreas containing islands could be found in the midst of the new growth in a sufficient amount to correspond to the unextirpated fifth. In this connection the possibility of an accessory pancreas (Thorel,[17] Sweet[18]) or other glands maintaining the balance of function must also be considered. v. Hansemann's explanation of the absence of glycosuria is not applicable unless we assume that all cancers of the pancreas arise from the cells of the islands of Langerhans.

Finally we have the cases with glycosuria. In one of these a true diabetes existed, in the other an intermittent glycosuria. The first is readily explained by the presence of an interacinar pancreatitis with involvement of the islands, a type of pancreatitis originally described by Opie in connection with diabetes and since observed by many investigators. It therefore appears that while cancer of the head of the organ with duct obstruction may frequently cause a chronic pancreatitis, glycosuria does not result unless the interacinar form with involvement of the islands develops. This naturally brings cancer diabetes into a common relation with pancreatic diabetes in general.

The case of intermittent glycosuria brings up the vexed question of alimentary glycosuria. It is well known that a normal individual may digest without disturbance from 150 to 250 grammes of sugar, but that an increase over this amount may lead to temporary excretion of glucose in the urine. This excretion, due to hyperglycemia, is the inevitable result of a sudden flooding of the circulation with an amount of glucose beyond that which the body is able at once to consume. On the other hand, in a number of abnormal conditions where there is no actual diabetes, an alimentary glycosuria may be produced by an amount of sugar which in the economy of the normal individual is easily consumed. Among the prominent conditions in which this occurs may be mentioned neuroses, traumatic or otherwise, organic nervous diseases, alcoholism, infectious diseases, exophthalmic goitre, hepatic and pancreatic disease. Is it not possible that this temporary excretion of sugar is due to some transient disturbance of the function of the islands brought about by vascular disturbances of the islands or by some toxic substance, perhaps of the nature of an autotoxin, affecting the secretion of these structures or temporarily throwing them out of function? In a destructive disease of the pancreas, as cancer, a certain number of the islands are necessarily destroyed; the remainder, however, may be sufficient under normal circumstances to furnish the necessary secretion, whatever it may be, essential to carbohydrate metabolism; but if overtaxed by an unusual injection of glucose, hyperglycemia and a consequent glycosuria might result. This explanation has occurred to me in connection with my case of cancer accompanied by intermittent glycosuria; and that it is not entirely hypothetical is indicated by the observations of Ssobolew,[19] confirmed by Herzog,[20] that in some cases of permanent diabetes the pancreas exhibits a great diminution in the number of islands, and in some cases, an entire disappearance. This deficiency, however, is far from proven, and in mentioning it I do not wish to be placed in the position of advocating a pancreatic origin for all forms of diabetes.

Conclusions—We have a definite basis for ascribing a certain portion of the cases of diabetes to lesions of the pancreas and ultimately to lesions of the island of Langerhans. As a result of the study here briefly outlined we can, I believe, include the permanent diabetes of cancer of the pancreas in this group. Further observations must be made before the intermittent glycosuria can be attributed to destruction of large numbers of islands. The absence of diabetes in cases of extensive involvement of the pancreas would appear to be due to the survival of small fragments of the pancreas including a sufficient number of islands to carry on their peculiar function. The persistence of the islands under the adverse conditions described supports the observation heretofore made concerning their anatomical independence, while their enlargement, suggesting as it does a compensatory hypertrophy, is corroborative of the theory that they have an independent special function.

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EXPERIMENTAL PANCREATITIS CONSIDERED IN ITS RELATION TO THE ACUTE FORMS OF PANCREATITIS IN MAN.

Presented before the Medical Society of the Greater City of New York, February 8, 1904, in a discussion of "Diseases of the Pancreas."

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The short space of time allotted me in this discussion will not allow a comprehensive statement of the many fruitful experimental researches having for their object the elucidation of the physiology and pathology of the pancreas. Various phases of the experimental investigations will, doubtless, be taken up by others who address you this evening; and I have therefore, with the approval of your president, decided to limit my remarks to a consideration of the acute lesions which may be produced experimentally. What we have gained by experiment in this field is practically a knowledge of etiology, and it is therefore more particularly the question of etiology that I will discuss. I will not hesitate moreover to compare the experimental lesions with the acute lesions seen in man, with the object as far as possible of correlating the knowledge gained by experiment and that gained by pathological study.

In any consideration* of the acute forms of pancreatitis we are confronted at the outset with the question of classification. The division into hæmorrhagic, suppurative and gangrenous forms as made by Fitz would appear to satisfy all demands. Some writers, however, speak of a necrotic form. This is of doubtful value, for all forms show more or less necrosis; indeed, in the hæmorrhagic form, especially that produced experimentally, necrosis is a constant and essential part of the process, though not always evident macroscopically. The possibility of pancreatic hæmorrhage without inflammation—the so-called pancreatic apoplexy—

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* In the preparation of this brief summary I have freely used the recently published work of Opie (Diseases of the Pancreas, Its Cause and Nature, J. B. Lippincott Co., 1903) and Flexner's description of the pathological anatomy of the pancreas (Transactions of the Congress of American Physicians and Surgeons, 1903, vi, 18); and I take this opportunity to acknowledge my indebtedness. I have not attached a bibliography. All references may be found in the bibliography of Opie's work.

is another debatable question which, in the present state of our knowledge cannot be definitely settled. It seems probable from our present point of view, that thorough histological examinations of such cases would furnish evidence of inflammatory changes and bring this lesion under the head of hæmorrhagic pancreatitis. Seitz, the last writer (1892) to make a careful study of this lesion is, however, opposed to this view and believes that some cases, at least, may be attributed to arterio-sclerosis.

Hæmorrhagic Pancreatitis.—The gross appearance of this form of pancreatitis—an enlarged organ with diffuse or mottled hæmorrhagic areas of varying color and greyish-white spots or streaks of fat necrosis—is so well known that we may turn at once to the question of etiology. Our knowledge of the causes of pancreatitis is entirely the result of experiments having for their object the reproduction of the condition. Clinical observations have contributed nothing, and with the exception of Opie's observations upon the relation of cholelithiasis, the same may be said of general pathological examinations. The simplest form of experimentation is the injection into the pancreatic duct of various irritating or supposedly injurious substances. A great variety of substances thus introduced have been found to produce typical hæmorrhagic pancreatitis, usually with fat necrosis. These substances are deliquescent zinc chloride (Thiroloix), artificial gastric juice (Hlava, Flexner and Pearce) bile (Opie, Flexner and Pearce), papaine (Carnot), and bacteria and their toxins (Hlava, Carnot, Flexner). Various other substances as formalin, nitric and chromic acids, and solution of caustic alkalies, Flexner found would produce the same results. The disease produced by these various agents usually runs a rapidly fatal course, though some animals may live for weeks and present at death extensive suppurative or sclerotic changes. In some instances putrefactive micro-organisms invade the injured organ and cause a gangrenous pancreatitis. If we study these various methods with the view of determining if any of them may operate to cause the hæmorrhagic pancreatitis seen in man, we have four possibilities: action of (*a*) ferments originating in the pancreas, (*b*) bacteria, (*c*) gastric juice, and (*d*) bile.

The possibility of the first is suggested by Carnot's experiments with papaine, and some support is offered by Chiari's observations upon autodigestion of the pancreas. According to Chiari this change occurs shortly before death and may be accompanied by multiple small hæmorrhages. The destruction of the parenchyma thus brought about affords an opportunity for the diffusion of the pancreatic ferments. There is some evidence that fat necrosis may be caused by the fat splitting ferment thus liberated, but as yet we have no definite proof that a true hæmorrhagic pancreatitis may result from the action of this or other ferments liberated at the same time.

Various micro-organisms, as the bacillus coli, the pneumococcus and the pyogenic cocci have been found, not infrequently, associated with hæmorrhagic pancreatitis. There has been no uniformity in these findings and most of the writers reporting the results of bacteriological examinations agree that the organisms represent a secondary invasion of injured tissue and are in no way concerned in the etiology of the lesion.

That the gastric juice, as suggested by Hlava may enter the pancreatic duct and produce an inflammation of the pancreas presupposes a powerful anti-peristaltic, or other action, forcing the secretion into the duct. Of such action we have no definite evidence. Under normal conditions it is practically impossible to force fluids from the intestine into either bile or pancreatic ducts. I have recently made some experiments upon dogs in order to determine this point. The intestine was ligated at varying distances above and below the orifice of the ducts and distended by injecting colored solutions and suspensions. After varying periods of time, the animals were killed, but no staining of the ducts could be demonstrated. In other experiments upon the dead animal, forcible manual pressure was exerted upon the similarly ligated intestine with negative results. On the other hand it cannot be denied that under certain pathological conditions of the duct orifice, intestinal fluids may possibly be forced into the duct. Concerning the negative action of the natural gastric juice upon pancreas parenchyma the following case would appear conclusive:

(*Records of the Pathological Department of the University of Pennsylvania; Autopsy No. 0.148.*) The clinical history of this case is brief and incomplete. The patient, a negro, aged forty-one, was admitted to the Insane Department of the Philadelphia Hospital on July 19, 1900, with a diagnosis of delusional insanity. For the next six months his condition, apparently, was not noteworthy. "On January 28, 1901, patient seemed to be rather dull and was put to bed." On February 11th, regurgitation of blood mixed with milk curds was observed. This continued until his death, on February 13th. Physical examinations revealed a rather firm mass in right hypochondriac region, which, upon palpation caused patient to complain of pain. At no other time did he complain of pain. Temperature normal, pulse about 100 and of poor volume; no distention of abdomen; marked constipation. Albumen was found in the urine; and microscopically, numerous hyalin and granular casts. The clinical diagnosis was cancer of the stomach and the liver with chronic nephritis.

Autopsy—Pathological diagnosis: Recent hæmorrhage in and about pancreas and duodenum, chronic gastro-pancreatic fistula; chronic interstitial pancreatitis; chronic pulmonary tuberculosis; tubercolosis of bronchial, gastro-hepatic and retro-peritoneal lymph nodes; chronic mitral endocarditis; general chronic passive congestion; chronic diffuse nephritis (parenchymatous type).

Abdominal cavity: Stomach greatly dilated, the lower margin extending below the umbilicus; pylorus touching right costal margin. Beneath the pylorus and entirely surrounding the duodenum is a globular, firm, hæmorrhagic mass, distinctly encapsulated and resting on the upper end of the right kidney. The subperitoneal tissues between the stomach and the transverse colon and in the neighborhood of pylorus and adjacent abdominal wall are infiltrated with clotted blood. Stomach, pancreas, duodenum and transverse colon with hæmorrhagic mass removed entire. Upon opening the stomach it is found to be normal except for the presence of a small orifice with smooth edges four centimeters from the œsophageal end. The outer wall of the stomach about orifice is bound to the pancreas nine centimeters from its splenic end by dense fibrous adhesions. A probe passed through the orifice in the stomach enters a sinus leading to the pancreas. This sinus passes directly through the pancreatic tissue. Its walls are lined by dense fibrous tissue, and it contains blood-stained mucus-like fluid. The canal can be followed for a distance of five centimeters. It then approaches the surface of the pancreas where it is continuous with the blood clot about the duodenum. No foreign body is found in the sinus. The splenic end of the pancreas for a distance of eight centimeters appears normal; the middle portion for a distance of four and a half centimeters is paler and firmer than normal, and the lobulations are not so distinct; through the remaining five centimeters constituting the duodenal end, the pancreas is extensively infiltrated with blood. Surrounding the duodenal end of the pancreas and completely encircling the duodenum is an encapsulated mass of black clotted blood fourteen centimeters in length and seven centimeters in diameter. The long diameter of this clot corresponds to the course of the duodenum. The source of the hæmorrhage cannot be discovered. The pancreatic and common bile ducts are patulous. The mucous membrane of the duodenum is very thin, blood-stained, and at one point presents a small adherent blood clot two centimeters in diameter. No fat necrosis.

Histological examination: The wall of sinus is composed of dense fibrous tissue. On its surface is a thin layer of granular material with a few pus cells. Sections stained by the Gram-Weigert method show a few cocci and bacilli. Scattered through superficial portion of sinus wall are many lymphoid and plasma cells and a few polymorphonuclear leucocytes. New blood vessels are seen throughout, and here and there are small areas of hæmorrhage. In the deeper portions the hæmorrhage is more diffuse, and here are seen small islands of atrophic pancreatic tissue infiltrated by lymphoid cells. From the sinus wall coarse bands of fibrous tissue run into the substance of the pancreas, and divide into finer lines which penetrate the pancreatic acini. Sections from various portions of the pancreas, at a distance from the sinus, show a moderate increase of perilobular connective tissue. The cells of the parenchyma are very granular and stain poorly. The islands of Langerhans are prominent and unaltered. Throughout the duodenal portion extensive hæmorrhage is seen in the interstitial tissue, penetrating in places the parenchyma which is œdematous. No necrosis or exudation is evident. The splenic portion is free from hæmorrhage.

From this description it is evident that in the early development of the sinus the gastric juice must have been in intimate contact with the pancreas parenchyma but failed to produce a hæmorrhagic pancreatitis. The hæmorrhage into the duodenal portion, was unaccompanied by acute changes and was due apparently to extension from the large clot about duodenum. The chronic pancreatitis was merely a localized process about the sinus. The case offers strong evidence against the possibility of gastric juice exciting a typical hæmorrhagic pancreatitis.

The relation of bile to acute pancreatitis has received very substantial support from experimental observations and also from the not unusual occurrence of the lesion with cholelithiasis. The most important contributions to this phase of the subject have been made by Opie, who has worked out the pathogenesis of pancreatitis associated with gall-stones and by injecting bile into the pancreatic duct of the dog has produced a typical inflammation of the gland with associated fat necrosis. In one particularly fortunate autopsy he found at the apex of the diverticulum of Vater a small calculus completely blocking the duodenal orifice but too small to obstruct the orifices of the common bile and the pancreatic duct. These ducts were thus transformed into a continuous closed channel from which it was impossible for their respective contents to escape. Upon dissecting the pancreatic duct it was found to be stained light green with bile, indicating that the slightly greater pressure in the bile duct, probably due to the contraction of the gall-bladder, had forced bile into it. An acute hæmorrhagic pancreatitis with disseminated abdominal fat necrosis existed.

The same writer has also analyzed the reported cases of acute pancreatitis and finds that cholelithiasis is very constantly associated with the hæmorrhagic and gangrenous forms of the lesion. On the other hand, acute pancreatitis is a rare condition as compared with the relative frequency of cholelithiasis. In this connection it is important to point out, as Opie has done, that in only a small proportion of individuals (in about three out of ten) are the anatomical features such as to allow favorable conditions for bile to penetrate the pancreatic duct. The ducts, in a considerable number of individuals (ten per cent.) open separately and the diverticulum does not exist. Also, the size of the diverticulum bears an important relation to the production of the condition; its variation in length is from zero to eleven millimeters; the average diameter of the orifice being two and a half millimeters. In only thirty of Opie's 100 examinations did the length reach five millimeters. Thus it is evident that a stone to produce obstruction of the duodenal orifice only, must be relatively smaller than the diverticulum, for otherwise the orifices of both ducts would also be obstructed and the secretions forced back upon their respective organs.

While cholelithiasis is thus definitely established to be an important factor in the etiology of acute pancreatitis, it does not explain all cases. Many cases have been reported in which neither clinical history nor autopsy affords evidence of cholelithiasis, though it is noteworthy that since attention has been called to this association these cases are not so numerous. It should also be noted in this connection that the stone after obstructing the papilla orifice and causing a pancreatitis may pass into the intestine and escape observation, or perhaps pass from the intestine entirely A dilatation of the diverticulum may in such cases indicate the previous resting place of the stone. The following case would appear to be an example of this kind:

Clinical abstract: Patient of Dr. W. E. Fay, of Boston, Mass.—Robust woman, aged thirty-six, with history of occasional sharp attacks of gastroenteritis after excessive indulgence in wine. "The mortal attack began with a 'French' dinner on Thanksgiving Day. From claret she changed to whiskey, drinking considerable between November 29th and December 8th. When first seen on the latter of these dates she was tremulous and sleepless, with wild look in the eyes, intense burning in epigastrium and violent and continuous emesis. Neither water nor cracked ice could be retained. The vomitus was green, thin and acid. After hypodermic use of morphine and careful administration of chloroform, almost steadily for an hour, sleep was obtained lasting three hours. Restlessness then returned, with frequent hiccough, and ceaseless cry for water, which was rejected in whatever quantity or temperature given. Washing of stomach, and paraldehyde administered by enema afforded temporary relief. Abdomen was distended. Obstinate constipation was overcome by high enemata. Persistent flatulence was present in both stomach and bowel, and considerable pain centering in the epigastrium and extending throughout the abdomen. This condition continued with temporary alleviations for nine days after she was first seen. Then, December 17th, slight jaundice was noticed. The patient desired nothing but frequent drinks of milk and limewater. December 20th the patient sitting up and begins to eat gruel, but has no energy. December 24th, sudden enlargement of right parotid and adjoining glands with redness extending below angle of jaw; considerable emaciation has taken place. After sitting up parts of two or three days, which was agreeable to her, there was increase of tenderness throughout the abdomen. Temperature rose to 101 degrees. Distention was constant, free fat appeared in the urine; sugar was present. The patient sank rapidly and died on the 30th."

Autopsy, performed six and one-half hours after death.

Anatomical diagnosis: Hæmorrhagic and gangrenous pancreatitis with fibrinous peritonitis and accumulation of grumous fluid in peritoneal cavity. Multiple fat necroses of omentum, mesentery, epiploic appendages and subperitoneal fat generally. Acute duodenitis with dilation of orifice of duodenal papilla. Localized dilatation of common bile duct. Dilatation of pancreatic duct. Fatty degeneration of heart, liver and kidneys. *Abdomen*—Excessive amount of subcutaneous fat. Omentum, mesentery, epiploic appendages and abdominal fat generally closely studded with round or oval greyish-white areas two to five millimeters in diameter and distinctly circumscribed. Many of the greatly enlarged epiploic appendages (3 x 1.5 cm.) are entirely necrotic. In pelvis and both flanks is a thin greyish-red greasy fluid containing small black shreds of friable material. Omentum is glued to anterior abdominal wall by a blood-stained fibrinous exudate. A similar exudate covers the coils of the small intestine. The position of the pancreas is occupied by a soft friable, irregular reddish-black mass 4 x 1.5 centimeters, freely moveable. The cavity in which this mass lies is lined by reddish-black necrotic tissue, which adhere in places to colon and stomach. The mass on section shows at splenic end irregular areas of greyish pancreatic tissue separated by dark red lines of hæmorrhage and necrosis. Elsewhere it is uniformly necrotic. *Duodenum*—Contains material similar to that about pancreas and its mucosa is injected. The orifice of papilla is dilated and in the duct one centimeter from the orifice occurs a circular dilatation with smooth walls, one and five-tenths centimeters in circumference. No calculi are found in gall-bladder, ducts or intestine. The pancreatic duct is dilated and separated from the pancreas; a probe from duodenal end passing directly into the cavity about the gangrenous pancreas. Bacillus coli was found in the necrotic material about the pancreas.

While this case is not conclusive, in as much as the stone was not found, the anatomical condition indicates that a calculus, at some time, was lodged in the common duct and the possibility of later occlusion of the papilla with final discharge of the stone is evident.

The Sequence of Histological Changes in Hæmorrhagic Pancreatitis.—Much discussion has arisen concerning the precedence and succession of the three principal phenomena—hæmorrhage, necrosis and exudation. Katz and Winkler believe that the necrosis follows hæmorrhage and is the direct result of injury produced by the extravasated blood. Hlava found extensive occlusion of the blood vessels after acid injection and considered it to be the cause of both necrosis and hæmorrhage. Opie found hæmorrhage intimately associated with necrosis and followed only secondarily by inflammatory changes. From his earlier experiments Flexner drew the conclusion that hæmorrhage and necrosis are the result of the simultaneous action of the injurious agent upon blood vessels and tissue, and that they occur coincidentally. In a later series of experiments by Dr. Flexner and myself an attempt was made to definitely settle these mooted points. Dogs under choretone narcosis received injections of one to two per cent. solutions of hydrochloric acid into the duct and directly into the parenchyma of the pancreas. Small portions of the organ were removed after periods varying from thirty-five minutes to eight hours and examined histologically. It was found that hæmorrhage, hyalin necrosis and exudation of fluid and leucocytes could be readily demonstrated in tissue removed one hour after injection. Sections taken at the end of eight hours represented the pathological process at its height. That these lesions are correlated in the pancreas may therefore be considered as demonstrated.

At the same time in order to determine the effect of red blood corpuscles upon the pancreatic tissue, a condition analagous to hæmorrhage was brought about by the injection of sterile defibrinated dog's blood through the duct and directly into the parenchymà. Such injections did not set up an acute pancreatitis but were followed by chronic proliferative changes. Similar injections of dog's serum were negative.

Gangrenous Pancreatitis.—Experimental and post-mortem observations both indicate that in the majority of cases gangrenous pancreatitis is secondary to an acute hæmorrhagic inflammation of the organ. The tissue, primarily the seat of hæmorrhage, necrosis and inflammation readily becomes gangrenous under the influence of putrefactive micro-organisms invading it from the intestinal canal. The association of hemorrhage and gangrene frequently seen at autopsy was first emphasized by Fitz, who also recognized however the possibility of the lesion originating from perforating inflammation of the gastro-intestinal canal or of the biliary passages.

In the series of experiments by Dr. Flexner and myself, two examples of gangrenous pancreatitis following acid and bile injections respectively, occurred. Death occurred in each instance in less than twenty-four hours, and the gangrenous portions of the pancreas were studded with emphysematous blebs. Films showed bacilli having the morphology of B. aerogenes capsulatus. Futhermore, gangrenous pancreatitis has the same relation to cholelithiasis as has the hæmorrhagic form. In Opie's table of thirty-seven cases of acute pancreatitis associated with cholelithiasis, eight are described as hæmorrhagic and gangrenous and thirteen as gangrenous. Disseminated fat necrosis is a striking feature of this lesion.

Suppurative Pancreatitis.—Suppurative inflammation of the pancreas, unlike the hæmorrhagic and gangrenous forms, does not differ essentially from that of other organs. It may be primary or secondary. The relation of the pancreas to the intestine allows the possibility of infection through the duct, while lesions of adjacent hollow viscera may extend directly or as the result of perforation. In general infection of the blood, pyæmic abscesses may develop in the pancreas as in other organs. Direct extension of an infectious pylephlebitis may also occur. These lesions are seldom accompanied by extensive necrosis, hæmorrhage or disseminated fat necrosis. The accumulation of pus is not diffuse but occurs usually as localized abscesses. Hæmorrhage and necrosis if present are generally focal in character, suggesting the local action of an irritant. Rarely the pancreas may be entirely destroyed and appear as a sequestrum in a pus cavity. Experiments, especially those of Flexner, show that abscesses of the pancreas may follow the injection of various fluids, as weak solutions of hydrochloric, sulphuric and nitric acids, sodium hydrate and suspensions of the B. pyocyaneus. In these experiments we have evidently a primary necrosis due to the irritant and a secondary invasion by micro-organisms. Körte, in a few instances, produced abscesses by injecting pus containing a bacillus of the colon group. These experimental lesions are seldom accompanied by fat necrosis. A study of the lesion in man and of the experimental findings indicates that this suppurative form of pancreatitis is due to some local influence causing limited necrosis and suppuration. There is, however, some evidence that duct obstruction may rarely lead to the condition probably in that it favors the entrance of bacteria. In Opie's table, previously quoted, "purulent pancreatitis" occurred in four of forty-one cases complicated by cholelithaisis. The common duct in only one of these, however, contained a stone. The following case illustrates suppuration of the pancreas with fat necrosis, accompanying cancer of the diverticulum and cholelithiasis:

Records of the Bender Laboratory, Autopsy No. 0.676. Clinical abstract: The individual, a male aged seventy-three, patient of Dr. A. W. Elting, was admitted to the Albany Hospital on August 24, 1903, with a history of hepatic colic which began on August 15th. Since May 1st he had suffered from gastric distress, nausea and dull pain in region of stomach, and had lost in strength and weight. Physical examination reveals a jaundiced, emaciated, feeble individual with evidence of arterio-sclerosis, enlarged heart and emphysema of the lungs. Upon palpation of abdomen a distinct irregular tumor mass was felt in the epigastrium; deep pressure elicited some tenderness. During patient's sojourn in the hospital there was slight change in his condition. The jaundice continued and nausea after the taking of food persisted. The pain subsided. Physical examination revealed nothing new. Emaciation and weakness progressed rapidly, and death occurred on September 11th.

Autopsy, by Dr. A. T. Laird, twelve hours after death.

Anatomical diagnosis: Cancer of the diverticulum of Vater with ulceration of duodenum and metastases in liver; dilatation of common duct and gall-bladder; cholangitis, gallstones free in colon; jaundice;

multiple abscesses of head of pancreas; peripancreatic fat necrosis; hæmorrhage into intestine; arterio-sclerosis.

The individual is extremely emaciated and jaundiced. In *duodenum,* about one and a half centimeters above duodenal papilla, is a circular ulcer three .centimeters in diameter with irregular edges and firm indurated bile-stained base. The base of the ulcer, five millimeters in thickness, rests upon the head of the pancreas to which it is intimately adherent and upon indurated lymph nodes. The tissues beneath the papilla are infiltrated by a dense greyish-white diffuse growth of new tissue. The duodenal papilla is prominent and rests on the indurated mass below it; bile readily flows from its orifice on forcible pressure of gall-bladder. Common duct is slightly dilated. Gall-bladder measures ten centimeters in length and is distended with thick fluid bile, no calculi present. *Liver* is of a dark uniform greenish color, and bile ducts are distended with thick bile. Scattered throughout the organ are numerous greyish-white firm areas, one-half to two centimeters in diameter, of fairly definite outline. *Pancreas* measures fourteen centimeters in length. The duodenal end for a distance of five centimeters is irregularly swollen. On section a yellowish purulent fluid escapes and the cut surface presents numerous abscesses of varying size with thin trabeculated walls. The middle portion of the organ is firmer than normal. Splenic end is unaltered. Duct patent though its proximal portion is surrounded by the new growth. Peripancreatic fat presents numerous distinctly circumscribed yellowish opaque areas. The small intestine is blood-stained throughout its length and contains an accumulation of blood, fluid and clotted. A lesser amount of blood is found in the large intestine. The source of the hæmorrhage is apparently the ulcer in the duodenum. In the lower portion of the discending colon are found two smooth facetted calculi composed of cholesterin and inspisstated bile. *Histological examination* shows a cancer about and involving the diverticulum and the common duct with extension to the duodenum and to the head of the pancreas and with metastases in the liver. The head of the pancreas is the seat of advanced perilobular pancreatitis, in the midst of which are numerous abscesses. These abscesses are chronic in character, and contain much necrotic material and zoogloea of large thick bacilli. The tail of the pancreas is the seat of a slight perilobular pancreatitis. Typical fat necroses are numerous. The ducts are dilated and contain an accumulation of mucous and desquamated epithelial cells.

Fat Necrosis.—This condition is so constantly a comcomitant of acute pancreatitis and its elucidation so entirely the result of experimentation that a consideration of the experimental lesions of the pancreas would be incomplete without reference to it. Hæmorrhagic and gangrenous pancreatitis, as they occur in man or as the result of experiment, are generally accompanied by this peculiar lesion of the fat tissue. Rarely it occurs in connection with suppurative lesions, and occasionally, as will be pointed out later, with chronic interstitial pancreatitis. The characteristic appearance is that of small round or oval areas white or greyish-white in color and usually sharply circumscribed. Microscopic examination shows these areas to be composed of necrotic fat cells. In early necroses fatty acid crystals may be demonstrated. These areas are found most abundantly in the neighborhood of the pancreas and are usually limited to the abdominal fat, but they may be widely disseminated and appear in the fat beneath the pericardium and the pleura, in the subcutaneous fat and in the marrow of long bones. Fitz first suggested that fat necrosis is the result of a lesion of the pancreas, but to Langerhans belongs the credit of first demonstrating the essential nature of the process. By chemical and histological studies he showed that the changes within the fat cells are associated with the splitting of the fat molecule into its fatty acid and glycerine. The glycerine is absorbed and the acids are deposited in the cells as needle-like crystals. The cell loses its nucleus and is apparently necrotic. Later, chronic proliferative changes occur about the areas. Leucocytes may enter the necrotic fat but when numerous, indicate invasion by bacteria. Although bacteria have been frequently found in these necroses they are not concerned in the production of the lesion and must be considered as secondary invaders. Instances in which the injection of bacteria into the pancreatic duct has resulted in the necrosis of fat are to be explained by the setting free of pancreatic ferments as the result of injury to or inflammation of the gland.

The first experimental proof of the relation of fat necrosis to pancreatic ferments was offered by Langerhans, who injected suspensions of the comminuted pancreas of the rabbit and dog into the perineal fat of the rabbit. One of his thirteen experiments was successful and he concluded that these necroses are due to the action of the fat splitting ferment of the pancreatic juice. Jung obtained similar results by introducing portions of the fresh pancreas of one animal into the adbominal cavity of another; Hildebrand and Dettmer, Williams, Whitney, Flexner, Milisch, Körte and Opie have obtained similar results by various injuries allowing the escape of the pancreatic juice into the adjacent fat and the peritoneum. Their methods include ligation of ducts and vessels; ligation, laceration and incision of the parenchyma; and excision of portions of the organ. The experiments of Hlava, Körte, Oser, Opie, Flexner and Pearce, in which an acute pancreatitis, usually hæmorrhagic, has followed the injection of various substances as acids, alkalies, gastric juice, bile, bacteria, etc., have also caused the appearance of fat necrosis. In these experiments the fat necroses are not due to the substance injected but to lesions of the pancreas which allow an escape of the pancreatic juice. The final link in this chain of experimental evidence was Flexner's demonstration, by chemical test, of the presence of a fat splitting ferment in the necrotic foci. Portions of the necrosed foci, from both human and experimental cases, when brought in contact with neutral butter fat caused a splitting of the fat with the freeing of fatty acids recognizable by their odor and reaction.

It has been claimed by some writers, especially by Oser, that the presence of a fat splitting ferment will not explain the widely disseminated necroses, such as occur in the sub-pericardial, sub-pleural, and sub-cutaneous fat. Opie has, however, in a series of duct ligations demonstrated by Flexner's method the presence of the fat splitting ferment in the distant necroses of the subcutaneous and subpericardial fat as well as in the peri-pancreatic foci. The diffusion of the ferment in these experiments he also found was hastened when the secretory activity of the pancreas was stimulated by injection of pilocarpine.

Wells (*Journal of Medical Research, 1903, ix., 70*) has found that commercial "pancreatin" will produce typical fat necrosis, but that this power is lost after heating for five minutes at some point between sixty-five and seventy-one degrees centigrade. Its power to produce fat necrosis decreases proportionally as the temperature is raised above fifty-five degrees Centigrade. These observations indicate an enzyme action as the source of the lesion. He was unable, however, to determine which of the pancreatic enzymes causes fat necrosis, and could not produce fat necroses with the lipolytic extracts of hog's liver or cat's serum used either alone or in combination with trypsin. He thinks it possible that the lipase causes fat splitting after some other ingredient of the pancreatic juice has injured the cell; fat splitting is subsequent to the necrosis and not its cause. The lipase normally in fat tissues exerts no fat splitting effect upon necrotic fat if the latter be preserved from external influences. Foci of fat necrosis became visible to the naked eye three to five hours after the application of "pancreatin" and were found outside the abdominal cavity as early as twelve hours after intraperitoneal injection.

In considering the application of the results of experimental fat necrosis to the lesion as seen in man, it must be borne in mind that fat necrosis bears the same relation to obstruction of the pancreatic ducts as jaundice does to hepatic obstruction. Obstruction to the outflow of the pancreatic secretion causes its diffusion into the surrounding tissues (Opie). The escape of the ferment in the acute lesions of the pancreas is readily explained by obstruction or destruction of the finer ducts or by injury to the parenchyma. On the other hand either temporary or permanent obstruction of the duct of Wirsung by calculi or by cancer may be accompanied by fat necrosis. Usually other lesions exist as suppurative or chronic pancreatitis but in a few cases, as those reported by Fraenkel (stone in diverticulum) and by Flexner (stones in common duct) no lesion of the pancreas was found. There can be little doubt that in these cases the calculus causes compression of the pancreatic duct and an accumulation of secretion which finally becomes diffused into the adjacent tissues.

The following case would appear to belong in this group. A chronic atrophic cholecystitis with atrophy of the bile ducts and adhesions to head of pancreas apparently caused pressure upon the pancreatic duct.

Records of the Bender Laboratory, Autopsy No. 0.614. Autopsy by Dr. A. T. Laird, seven and one-half hours after death; female, aged forty-two.

Anatomical diagnosis: Extensive syphilitic ulceration of nose and palate, œdema of lungs, hydrothorax, chronic cholecystitis with almost complete obliteration of gall-bladder and ducts, fat necrosis of pancreas. The gall-bladder is greatly atrophied and lies in a mass of dense fibrous adhesions which bind it to the duodenum and the head of the pancreas, and which also surround and penetrate the foramen of Winslow. The cavity of the gall-bladder measures but two centimeters in diameter. The pancreas measures 17 x 4 x 2 centimeters. At its head, the capsule is much thickened by adhesions binding it to the gall-bladder and to the duodenum. Over its entire surface numerous greyish-yellow opaque areas, not extending into pancreatic tissue, are seen. The consistence of the pancreas is normal.

Histological examination of the pancreas reveals numerous fat necroses, and dilated ducts filled with hyaline and granular material, desquamated cells and a few polymorphonuclear leucocytes. The latter also, to a moderate degree, infiltrate the walls of the larger ducts. No inflammation of the parenchyma proper is evident. The islands of Langerhans are unaltered.

The following accidental finding in a dog indicates that fat necrosis may follow a simple thickening of the orifice of the duct:

"Dog 84—weight 8650 gramms.—Isolated February 6th.—Urine normal on February 7th and 8th. Killed on February 12th for purpose of obtaining organs for injections in connection with cytolytic work. All organs normal except pancreas, the capsule of which is studded with numerous small greyish-yellow areas of definite outline and of firmer consistence than surrounding pancreatic tissue. No evidence of acute or chronic inflammation. No fat necroses of abdominal fat elsewhere. No obstruction of the duct is found. The papilla of duodenum, however, appears as a distinctly elevated, swollen, greyish-yellow ring; a sharp contrast to the normal appearance. A fine probe passes readily into the duct. The second pancreatic duct is not found. The orifice of bile duct, lying one and a half centimeters above pancreatic duct, can be located only by forcing bile from the gall-bladder. Histological examination shows fat necroses, chronic in character; pancreas otherwise normal."

Finally, as pointed out by Opie, we have fat necroses associated with cases of chronic intestitial pancreatitis in which duct obstruction by calculi is not present. Here it is probable that the newly formed fibrous tissues contracts about the smaller ducts, constricts them, and allows an accumulation of secretion which finally diffuses into the adjacent tissues. These necroses are most apt to be parapancreatic. I have found two examples of this condition in the autopsy reports of the Bender Laboratory; in one associated with localized chronic interstitial pancreatitis, in the other with atrophy and lipomatosis. Macroscopic evidence of duct obstruction did not exist. These reports are as follows:

No. 0.223. Autopsy twelve hours after death. Male, aged forty nine.

Anatomical diagnosis: Acute follicular duodenitis and ileitis; acute swelling of spleen and mesenteric lymph nodes; fatty degeneration of liver; arterio-sclerosis; atrophy of pancreas with lipomatosis, auto-digestion and foci of fat necrosis; general infection with the bacillus of Friedländer. The *pancreas* appears to be of normal size, but much of the parenchyma is replaced by diffuse masses of fat tissue. On section small islands of pancreas are seen widely separated by fat tissue. This change is most marked at splenic end where little pancreatic tissue remains. The parenchyma in some areas is whiter and softer than normal, and in other places presents a reddish-brown appearance, suggesting minute hæmorrhages. On the surface and on section several, minute, opaque white points suggesting fat necrosis are seen. No calculi are found in the ducts; the vessels present a few small areas of atheroma.

Histological examination shows small islands of pancreas widely separated by adipose tissue, slight self-digestion of these areas, and typical foci of fat necrosis with minute hæmorrhages. The interlobular connective tissue is increased in amount; the small ducts dilated and some acini appear as duct-like spaces with flattened epithelium and contain a finely granular material. In some islands these altered acini are very abundant and apparently indicate atrophy from pressure within the lumen. The islands of Langerhans are unaltered.

No. 0.382. Autopsy ten hours after death. Male, aged sixty three.

Anatomical diagnosis: Arterio sclerosis, hypertrophy and dilatation of heart; general passive congestion; œdema; double hydrothorax; thrombus of right auricular appendage; multiple infarcts of lungs; fat necrosis of pancreas. *Pancreas* twenty centimeters long. Twelve centimeters from the tail, over an area two and a half centimeters in diameter, the capsule is greatly thickened; beneath the capsule the pancreas presents a congested area containing many small yellowish-white areas of soft cheese-like consistence. A few similar areas are found elsewhere in the pancreas.

Histological examination reveals a slight localized interlobular pancreatitis, with typical fat necrosis.

It is possible that the first of these cases belongs to the group described by Chiari, in which, in his opinion, self digestion of the pancreas occurs shortly before death as an agonal change and allows the escape of the fat splitting ferment and the development of fat necrosis with associated minute haemorrhages. That fat necroses may develop very quickly is shown in one of the experiments of the series carried out by Dr. Flexner and myself, in which necroses were evident eight hours after injection of a one per cent. solution of hydrochloric acid into the pancreatic duct. Wells has observed their occurrence three to five hours after the application of "pancreatin."

The theory that postmortem digestion of the pancreas may set free the pancreatic secretion and allow the development of fat necrosis has little evidence to support it. In connection with these agonal necroses Opie believes it is possible that shortly before death, owing to alterations in the character of the pancreatic juice, it may become thick and viscid, in consequence of which it flows slowly. Stagnation and slight diffusion of the secretion may result and cause the insignificant necroses occasionally seen.

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SYMPOSIUM ON DIABETES *

I. THE PATHOLOGY OF DIABETES.

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As it will be impossible in the short time at my disposal to cover all phases, many of them little understood, of the pathology of diabetes; and as the questions of chemistry and metabolism are to be discussed by Dr. Edsall who has specialized in these fields, I have determined to limit my remarks to a consideration of the pathology of that form of permanent diabetes, which, in the light of recent investigations, appears to be dependent upon lesion of the pancreas.

We may for the moment disregard the various forms of temporary glycosuria, variously known as alimentary, nervous, renal, and hepatic glycosuria and devote our attention to the permanent form, which, owing to its obscure etiology and the severe nutritional disturbances by which it is accompanied, the difficulties of treatment and the universally fatal termination has been the object of constant observation and investigation.

The literature of diabetes is replete with hypotheses and theories of the most divergent and conflicting character; but throughout this literature may be seen the tendency to associate diabetes with an altered physiology of the pancreas. This is due undoubtedly to the important function which this organ plays in the metabolism of carbohydrates, but also in no small degree to the frequency with which gross lesions of the pancreas are found in persons dying of the disease. Thus of the early English cases, Cawley† (1788), reports pancreatic calculus with atrophy of the gland; Bright (1833), cancer of the head of the pancreas with duct obstruction and

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* Part of a Symposium on Diabetes, read before the New York State Medical Society at Albany, January 26, 1904.

† As the literature of diabetes has been so recently collected by Opie in his book, Diseases of the Pancreas, a work which has been freely used in the preparation of this summary, I have not attached a bibliography.

consequent atrophy. The first definite statement of such a relation appears to be that of Bouchardat (1785), which received considerable support from both French and English writers. General support, however, was lacking, and the German medical world especially, did not concur until the publication of the convincing extirpation experiments of v. Mering and Minkowski. In these experiments it was found that complete removal of the pancreas is followed always by a definite diabetes of severe grade. Glycosuria appears as early as six hours after the operation; the sugar gradually increasing until the third day when it is usually about eight or ten per cent., though twenty-two per cent. (Hedon) has been observed. Towards the end, these high percentages fall, and as the sugar reaches its minimum, diacetic acid, acetone and oxybuturic acid appear in the urine. The other symptoms of diabetes are present, as hunger, thirst, and loss of weight. The animals ultimately succumb after varying periods of progressive emaciation and weakness. A repetition of these experiments upon a variety of animals has yielded uniformly concordant results. In birds glycosuria does not occur but the blood shows a considerable increase in its sugar content (hyperglycemia). Diet has but a slight modifying effect. While the maximum sugar elimination naturally occurs with a carbohydrate diet, an albuminous diet does not reduce it below five or six per cent., while fasting for seven days does not cause its entire disappearance. Moreover, it was found that if one-fourth or one-fifth of the pancreas was allowed to remain diabetes did not result; nor did it result, if after complete extirpation, a portion of the pancreas was transplanted subcutaneously. These experiments demonstrated conclusively a specific relation between some function of the pancreas and carbohydrate metabolism. What this function might be, or what changes in the pancreas might disturb its equilibrium was not clear. It was evident, however, that it could be explained only by an internal secretion, for no disturbance followed ligation of the duct. Furthermore it was evident that no other organ could vicariously assume this function of the pancreas.

Stimulated by these experiments, interest in the pancreas was renewed and as a result much data concerning the pathology of the pancreas of diabetes came to hand. Seegen, Hansemann, Dieckhoff and Williamson reported the results of large series of cases. In these, as well as in those previously reported by Windle, Frerichs and White, definite lesions of the pancreas occurred in a very large proportion of the cases. This relation is strikingly shown in the tabulations of Oser. Calculus of the duct with secondary atrophy stands out as a prominent condition. Cancer of the head with like atrophy was not uncommon. In Hansemann's series simple atrophy was present in thirty-six of forty cases. Other conditions found were chronic pancreatitis and lipomatosis.

Still many cases of diabetes constantly came to notice without lesion of the pancreas. Naunyn, indeed, in a series of forty autopsies found only one case in which the disease could be ascribed to disease of the pancreas. On the other hand, many cases of grave disease of the pancreas without diabetes were observed; Hansemann reports such a case in which complete destruction of the pancreas existed. This anomalous condition he attempts to explain by the hypothesis that in primary cancer of the pancreas the cells of the new growth retain, in part at least, the function of the cells from which they are derived and that therefore the internal secretion is not disturbed.

At the same time various attempts were made to associate with diabetes some distinct histological picture; as the combined chronic pancreatitis and arterio-sclerosis of Hoppe-Seyler and Fleiner, and the perivascular sclerosis of Lemoine and Lannois. An important condition observed by the latter was the penetration of the fibrous strands into the acini, thus separating the cells and presenting a condition which they designated unicellular sclerosis. Hansemann particularly associated with diabetes a condition of the pancreas which he calls granular atrophy but which from his description appears to be a primary chronic pancreatitis with atrophy.

The most important contributions to the histology of the pancreas of diabetes are those made during the past few years by Opie. He distinguishes two forms of chronic pancreatitis; (1) interlobular pancreatitis, characterized by the formation of fibrous tissue between the lobules, which are often invaded from the periphery and (2) interacinar pancreatitis, in which the newly formed fibrous tissue is diffusely distributed within the lobule, separating the acini and invading the islands of Langerhans. With the first type, frequently associated with duct obstruction, diabetes occurs only in those relatively uncommon cases in which an advanced sclerosis involves the islands. With the interacinar type, however, diabetes is much more frequent. Another important change observed by the same writer is a hyaline transformation of the islands with little or no alteration of the secreting parenchyma. He therefore looks upon involvement of the islands of Langerhans as the important point in the pathology of diabetes. His figures support this view; in twenty-one cases of interlobular pancreatitis, diabetes occurred but once and in this case the advanced sclerosis had produced alterations of the islands; while in seven of nine cases of the interacinar type, diabetes coexisted; and in six of nineteen cases of diabetes, hyaline transformation of the islands was present.

Such observations imply that the islands are in some way concerned in carbohydrate metabolism and therefore of fundamental importance in any consideration of the etiology of diabetes. The occurrence of these lesions in diabetes has been confirmed by Weichselbaum and Stangl, Herzog, Gentes, Wright and Joslin, Curtis[1], Finney[2], Schmidt, Hansemann and Herxheimer[3]. The last three writers, however, are not prepared to admit that these changes are of etiological importance.

In this connection the following notes of five cases of diabetes and one of acute glycosuria, studied during the past two years, may be of interest:

I. Records of the Pathological Laboratory, University of Pennsylvania, Autopsy No. 01.212. Female, aged sixty-two years. *Clinical diagnosis*—Diabetes, moist gangrene of leg, tetanus. *Anatomical diagnosis*—Thrombosis of left iliac artery and its branches; softened thrombi in left auricular appendix; moist emphysematous gangrene of left leg; infarction of spleen and left kidney; chronic obliterative pericarditis; chronic mitral endocarditis; hypertrophy of left ventricle; chronic diffuse nephritis; chronic interstitial pancreatitis; chronic adhesive pleuritis. *Histological examination*—Interacinar pancreatitis with involvement of many of the islands of Langerhans by the invasion of dense bands of fibrous tissue.

II. Records of the Pathological Laboratory, University of Pennsylvania, Autopsy No. 01.309. Male, twenty-seven years. (Service of Dr. J. H. Musser, University Hospital.) *Clinical diagnosis*—Phthisis pulmonalis, diabetes mellitus, Banti's disease. History of diabetes of two years' duration; sugar varied in amount from 1.25 to 7.5 per cent.; specific gravity of urine 1028 to 1040. *Anatomical diagnosis*—Splenomegaly; slight chronic interstitial hepatitis; general tuberculous peritonitis; tuberculosis of lung (caseous and gelatinous pneumonia with cavity formation); tuberculous pleuritis; slight chronic mitral endocarditis; fatty degeneration of heart and kidneys. *Pancreas*—The surface is more nodular than normal, the depressed portions œdematous. On section the nodular appearance is very marked. The consistence is about that of the normal pancreas. *Histological examination* reveals a moderate perivascular fibrosis and a hyaline degeneration of many of the islands; approximately one of every five is hyaline.

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[1] *L'Echo Med. du Nord*, 1902, vi, 140.

[2] *The Medical Chronicle*, 1903, v, 137.

[3] *Orth-Festschrift*, 1903, s. 38.

III.—Records of the Pathological Laboratory, University of Pennsylvania, Autopsy 02.16. Male, aged thirty-eight years. (Service of Dr. Alfred Stengel, University Hospital.) *Clinical diagnosis*—Diabetes, tuberculosis. *Anatomical diagnosis*—Gangrene and multiple abscesses of lungs; acute fibrinous pleuritis; fatty degeneration of heart and liver; cloudy swelling of kidneys; slight atrophy of thyroid gland; chronic interstitial pancreatitis; fibrosis and caseation of right adrenal; arterio-sclerosis; acute splenic tumor; multiple superficial erosions of the œsophagus. *Pancreas*—Weight seventy grammes, smaller than normal and firmer. The shape is more distinctly triangular than usual. The surface of the pancreas is grossly nodular. *Histological examination* of the pancreas reveals a slight diffuse increase of connective tissue; the islands of Langerhans are normal. The right adrenal is almost completely destroyed by tuberculous caseation, and newly formed fibrous tissue. A small ganglion adjacent to the adrenal is not involved in this process. Left adrenal is normal. The alveoli of thyroid gland are moderately dilated.

IV.—Case of Dr. Wm. Pepper, of Philadelphia, presenting a history of nephritis, uræmia and acute (terminal) glycosuria. The autopsy report is not available. For sections of the pancreas and for the laboratory report which latter, owing to the peculiar terminal character of the glycosuria is given in full, I am indebted to Dr. Pepper. *Clinical history*—Female, aged fifty-eight, admitted to the University Hospital, September 4, 1902. " Patient in a semi-delirious condition and cannot give a satisfactory history of herself. From her daughter it was learned that the patient had been complaining of headache, dizziness and defective vision for the last two weeks, and that during the past week she has been at times quite delirious. On admission catheterized; urine slightly cloudy, dark amber; no precipitate; specific gravity 1025; albumen 1-15 by bulk (centrifugated); *no sugar;* no bile, indican negative; diazo not made; a few flat round epithelial cells, a few pale and dark granular casts, and a few white blood cells. *Sept. 5th*—Mental condition better. Bowels moved freely. Urine dark amber; slightly cloudy; very light flocculent precipitate; specific gravity 1030; distinctly acid; albumen 1-15 by bulk (centrifugated); *no sugar;* bile and indican negative; a few flat and round epithelial cells, few white blood cells, many pale and dark granular casts. *Sept 6th—Blood*—Hæmoglobin, eighty-nine per cent.; red cells 5,010,000; white cells 10,860; Widal negative; no malaria parasites; nothing abnormal in stained films. Urine 9 A. M. dark amber; slightly cloudy; light, flocculent precipitate; specific gravity 1029; distinctly acid; albumen 1-15 by bulk (centrifugated); *no sugar;* bile and indican negative. Many flat and round epithelial cells, a good many white blood cells, very many very short, pale and dark granular casts, a few waxy casts. 5 P. M. urine color changed to a very pale amber; slightly cloudy; no precipitate; specific gravity 1029; distinctly acid; a decided trace of albumen; *sugar* 0.83 per cent. by Fehling's test; bile and indican negative; sediment shows many short pale and dark granular casts, a few waxy casts, very many flat round and spindle epithelial cells, very many white blood cells, many mixed urates. *Sept. 7th*—Urine 11 A. M. pale amber, slightly cloudy; light flocculent precipitate; specific gravity 1031; distinctly acid; decided trace of albumen; *sugar* 0.83 per cent.; bile and indican negative. Many short pale and dark granular casts, few waxy casts, many flat spindle and round epithelial cells, many white blood corpuscles, many mixed urates. *Sept. 8th*—Urine 2 P. M. pale amber; hazy; specific gravity 1030; acid; *sugar* present in large quantities; decided trace of albumen; epithelial cells, urates, no casts. *Histological examination*—of the pancreas shows irregular foci of slight interacinar pancreatitis with distinct involvement of the islands of Langerhans. The islands are frequently enlarged; the fibrous tissue abundant and often somewhat hyaline in appearance; the cells compressed and indistinctly outlined.

V—*Bender Laboratory Records, Autopsy 0.726.* Case of Dr. Andrew MacFarlane, Albany, N. Y. *Clinical abstract*—Male, aged twenty-six; laborer, duration of diabetes about eight months. Sugar constantly present in urine rising at times as high as four per cent.; diacetic acid and acetone also present. *Autopsy*—The abdominal viscera only were examined through a limited incision. *Pancreas*—Apparently normal in its gross appearance. *Histologically,* scattered areas of interacinar pancreatitis are found. The islands present a slight but definite increase of connective tissue with moderate atrophy of the intervening cells. A few small areas of fat necrosis exist.

VI—Records of the Pathological Institute, University of Leipzig, Autopsy 98 (1898).* Female, aged twenty-six years. *Clinical diagnosis*—Diabetes, pneumonia. *Note of post-mortem examination*—Extreme sclerosis and atrophy of the pancreas with presence of calculi (weight of pancreas, fifty-four grammes); diffuse lobular pneumonia with fibrinous pleuritis; hydro-pericardium; cloudy swelling of liver; fatty degeneration of kidney; calcareous bronchial lymph nodes. *Histology of pancreas*—Extensive atrophy and chronic pancreatitis of the interlobular type. In the more sclerotic portions the growth of connective tissue is interacinar. The islands are few in number, small, often isolated and frequently invaded by fibrous strands.

Lesions of the islands occurred in five of these six cases; in one the change was of the nature of a hyaline transformation; in the other four an interacinar pancreatitis with involvement of the islands existed. Whether or not the glycosuria in case III, in which the pancreas was normal, was dependent upon the lesion of the adrenal it is impossible to say. Glycosuria does not usually accompany such lesions. On the other hand the experiments of Blum, Herter and Richards indicate that the adrenal is in some way concerned in carbohydrate metabolism. These investigators found that after the injection into animals of the adrenal gland or adrenal extract, a temporary glycosuria results. Herter and Richards produced the same result by painting the surface of the pancreas with the extract. These experiments, however, are not analogous to destruction of the adrenal.

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* For the privilege of reporting this case, I am indebted to Prof. F. Marchand of the University of Leipzig.

I can at this time also give a preliminary report of an investigation, as yet incomplete, of the diabetes associated with cancer of the pancreas. It is well known that cancer of the pancreas may or may not be accompanied by glycosuria. We have no definite explanation of the condition under which it occurs, though a resume of the literature shows that it is most common when the tumor is in the head of the pancreas and by duct obstruction causes atrophy (chronic pancreatitis) of the distal portion of the organ. The reverse condition, complete destruction of the gland by cancer without diabetes, is likewise difficult of explanation. It is true that Hansemann has suggested that the function of internal secretion is preserved by the cells of the new growth; but this is not applicable to secondary tumors and if we accept the theory that the islands alone furnish the internal secretion it is not tenable, as pointed out by Ssobolew and Opie, unless we assume that all primary tumors of the pancreas have their origin in the islands, and in support of this last possibility there is little evidence. Nicholls[4] has reported a primary adenoma of an islands, and Fabozzi[5] has recently described several primary cancers of the pancreas which he believes to have arisen from a like source. Fabozzi's observations, however, are not conclusive and are entirely opposed to the great mass of work on this subject.

I have been able to collect for study thirty cancers of the pancreas. Three of these were accompanied by glycosuria, which in one case was a true diabetes, and in the second an intermittent glycosuria. I have no data concerning the character of the glycosuria in the third case. In the first case the tumor was in the head of the pancreas, causing obstruction of the duct with chronic pancreatitis of the distal portion of the organ. This chronic inflammation was for the most part interlobular, but in places was of the interacinar type with involvement of the islands, that is, presented the lesion which, according to our new ideas is supposed to be essential to the occurrence of diabetes. The third case was unsatisfactory for study inasmuch as only the tumor had been preserved and observations concerning the condition of the uninvolved pancreas could not be made. In the second case, accompanied by intermittent glycosuria, the pancreas showed no noteworthy change in the uninvolved portion of the organ. This case, similar to those reported by Wille, brings up the vexed question of alimentary glycosuria. It is known that a normal individual may digest without disturbance from 150 to 250 grammes of sugar, but that an increase over this amount may lead to temporary excretion of glucose in the urine. This excretion is due to hyperglycemia, the inevitable result of a sudden flooding of the circulation with an amount of glucose beyond that which the body is able at once to consume. On the other hand, in a number of abnormal conditions where there is no actual diabetes, an alimentary glycosuria may be produced by an amount of sugar which in the economy of the normal individual is easily consumed. Among the prominent conditions in which this occurs may be mentioned neuroses (traumatic and other forms), organic nervous diseases, alcoholism, infectious diseases, exophthalmic goitre, hepatic and pancreatic disease. Is it not possible that this temporary excretion of sugar is due to some transient disturbance of the function of the islands brought about by vascular disturbances of the islands or by some toxic substance, perhaps of the nature of an autotoxin, affecting the secretion of these structures or temporarily throwing them out of function? In a destructive disease of the pancreas, as cancer, a certain number of the islands are necessarily destroyed; the remainder, however, may be sufficient under normal circumstances to furnish the necessary secretion, whatever it may be, essential to carbohydrate metabolism; but if overtaxed by an unusual ingestion of glucose, hyperglycemia and a consequent, glycosuria might result. This explanation has occurred to me in connection with my case of cancer accompanied by intermittent glycosuria and that it is not entirely hypothetical is indicated by the observations of Ssobolew, confirmed by Herzog, that in some cases of permanent diabetes the pancreas exhibits a great diminution in the number of islands and in some cases an entire disappearance.

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[4] *Journal of Medical Research*, 1902, viii, 385.

[5] *Ziegler's Beiträge*, 1903, xxxiv., 199.

This functional deficiency, however, is far from proven, and in mentioning it I do not wish to be placed in the position of advocating pancreatic origin for all forms of diabetes. We have a definite basis for ascribing a certain portion of the cases of diabetes to lesions of the pancreas; but here we must rest until an increase in our knowledge allows further conclusions. It is probable as suggested by Naunyn that with the pancreas other organs preside over carbohydrate metabolism, though perhaps in a less degree, and that the pancreas may act vicariously for them, although their function may not be sufficient to be substituted for that of the pancreas.

Another point brought out by this investigation of cancer of the pancreas is the resistance of the islands to invasion or obliteration by the new growth and the accompanying sclerotizing inflammation. Numerous unaltered islands were frequently seen in the fibrous tissue at the margin of the growth where the acini had been completely destroyed; moreover, these structures, both at the edge of the tumor and in distant portions of the organ, were often three to five times larger than normal. This persistence indicates the resistance of the islands and the increase in size suggests a hypertrophy possibly compensatory in character. No cases of complete involvement of the organ by cancer similar to those of Litten and Hansemann were seen; in the few instances of extensive invasion a sufficient amount of the organ, by analogy with the partial extirpation of v. Mering and Minkowski, remained to carry on the internal function of the gland.

Whatever the ultimate explanation of diabetes may be, it must be admitted that our knowledge of pancreatic diabetes has been largely extended by the recent studies of the islands of Langerhans. And here it may be pertinent to inquire what evidence have we that the islands from their anatomy, development and appearance in diseases other than diabetes are independent structures concerned in carbohydrate metabolism.

From the discovery of these structures by Langerhans in 1869, until within a few years, many and varied efforts have been made to explain their origin and function. They have been regarded from time to time as nervous elements, primary ducts, embryonic remains and as immature or wasted acini. The study of the ductless glands is largely responsible for the recognition of the similarity of structure of the islands and these organs. The structure of the islands—columns of cells rich in protoplasm, lying in an abundant vascular network of a sinusoidal character and with no excretory duct—

naturally suggests as their function the elaboration of some substance destined to be introduced into the circulation. This theory of the independence of the islands, first advanced by Shäfer, received considerable support from the experiments of Ssobolew. He found that after feeding animals on carbohydrates the islands became granular, indicating, according to his interpretation, a greater functional activity due to the increased demand for a ferment essential to carbohydrate metabolism. Furthermore he found that in the sclerotic atrophy following ligation of the ducts in animals the islands are not implicated and glycosuria does not result. These observations have been confirmed by Schulze. A similar persistence is frequently seen in the human pancreas in the sclerosis following duct obstruction; and has also been observed by Schlesinger, Opie, Condon[6] and myself[7] in the peculiar fibrous induration of the organ which occurs, not infrequently, in congenital syphilis.

Again, in the embryonic development of the islands we have evidence that they are destined for some special function. As I have recently demonstrated[8], the islands at an early stage of the growth of the pancreas arise from the primary acini and for some time remain connected to these structures by a solid process of cells; but eventually become entirely separated, and with the development of a blood supply proportionally greater than that of the acinus, become anatomically independent. Such anatomical differentiation argues for a special function, and taking into consideration the recently accumulated knowledge, the result of pathological investigation, we are forced to the conclusion that this function is an internal secretion concerned in carbohydrate metabolism and therefore of fundamental importance in any consideration of diabetes. This, however, is not equivalent to saying that all forms of diabetes may be traced to functional or structural changes of these structures. Fully one-half of the reported cases studied with regard to lesions of the islands show no alteration of these structures. That several forms of diabetes exist and that other organs than the pancreas are concerned in their etiology is evident; but this does not detract from the value of our recently acquired knowledge of pancreatic diabetes. The manner in which the hypothetical internal secretion of the islands is supposed to act comes under the head of chemistry and metabolism and will doubtless be considered by Dr. Edsall.

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[6] *Trans. Chicago Path. Society*, 1899-'01, iv., 200.

[7] *American Medicine*, 1903, vi, 1020.

[8] *American Journal of Anatomy*, 1903, ii, 445.

A consideration of diabetes would be incomplete without a consideration of the forms of glycosuria apparently dependent upon changes in organs other than the pancreas. As little however has been added in recent years to our knowledge of these conditions, I will speak of them but briefly. The forms of glycosuria associated with acromegaly, with cirrhosis of the liver, with arterio-sclerosis, and especially the diabetes of hæmochromatosis, in the light of recent investigations would appear to have a relation to disease of the pancreas.

Thus in acromegaly chronic inflammation of the pancreas has frequently been found at autopsy and it is probable as suggested by Opie, that "induration presumably analogous to that which acromegaly causes elsewhere occurs also in the pancreas and where sufficiently advanced produces glycosuria or even permanent diabetes."

The frequency with which arterio-sclerosis is associated with diabetes renders it probable that this condition by affecting the nutrition of the pancreas may be the cause of changes, inflammatory or sclerotic in nature, leading eventually to diabetes.

That the diabetes accompanying cirrhosis of the liver may, in many cases, be due to a coincident chronic pancreatitis, the result of a common etiological agent is indicated by the studies of Lefas, Opie and Steinhaus[9]. A more striking example of the dependence of chronic lesions of the liver and the pancreas upon a common etiological factor is hæmochromatosis (*diabête bronzé*). This condition, first described by v. Recklinghausen, is characterized by the extensive deposition of an iron-containing pigment in the cells of various organs and tissues, and is associated with a necrosis of the parenchymatous cells and a proliferation of the stroma. The liver and pancreas suffer most, the former being the seat of a hypertrophic cirrhosis, the latter of a chronic pancreatitis. The diabetes occurring in this condition has been explained by some writers as the result of the blood destruction, by others as the result of the pancreas lesion. Opie, in one case, found the inflammation to be of the intracinar type with involvement of the islands of Langerhans; and therefore concludes that this lesion is responsible for the occurrence of diabetes. In his case, however, diabetes did not exist owing to the incomplete destruction of the islands; the patient dying of typhoid fever before the disease had reached its height.

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[9] *Deutsch. Arch. f. Klin. Med.* 1902, lxxiv.

It is well established that glycosuria, temporary or otherwise, may follow lesions of the central nervous system and perhaps also of the sympathetic and larger peripheral nerves. Claude Bernard's classical *piqûre* of the floor of the fourth ventricle in animals, lesions (haemorrhage, tumor and softening) of the same location (medulla) and various pathological changes of the brain and cord in man illustrate this relation. We have, however, no definite information and Naunyn's theory that through the secretory or nutritive nerves we have a disturbance of function in the organs presiding over carbohydrate metabolism, is as satisfactory as any other.

In experimental phloridzin diabetes it has been demonstrated that a true hyperglycemia does not exist and that the glycosuria is due to an injury of the renal epithelium which allows an escape of the sugar normally present in the blood. An analogous condition (renal diabetes) in man has been suspected but not proven.

The influence of the adrenal gland upon carbohydrate metabolism has already been mentioned.

The relation of the thyroid gland to glycosuria is unexplained. Hansemann has collected fifteen cases in which diabetes and exophthalmic goitre were associated. Alimentary glycosuria is also frequently seen in this condition, according to Chvostek in sixty-nine per cent. of all cases; and it has also been observed after the therapeutic use of thyroid extract. It is worthy of note, however, that in none of the cases of diabetes associated with exophthalmic goitre has the condition of the pancreas been studied (Opie).

I have attempted to place before you in this brief summary the relation of the pancreas and especially the islands of Langerhans to diabetes. If I have dwelt too strongly upon this point it is because the knowledge of this relation enables us to sharply separate at least one form of diabetes from all others, and thus offers a definite point of departure for the study of those forms of glycosuria which, from our knowledge of the complexity of carbohydrate metabolism, we assume may be due to disturbances of other organs.